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ORIGINAL ARTICLES

THE PATHOGENESIS OF THE "VERNIX MEMBRANE"

Relation to Aspiration Pneumonia in Stillborn and Newborn Infants

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THE pathogenesis of aspiration pneumonia in newborn infants remains a controversial matter with opinions about equally divided as to whether the pneumonic process is caused by the aspiration of the infected contents of the amniotic sac and vagina or by chemical irritation of the lung by meconium, vernix and amniotic fluid.[1-4] Since both of these opinions have been based to a large extent on assumptions, an attempt has been made in this study to obtain evidence which would help to determine more precisely the effect of aspirated meconium, vernix and amniotic fluid on pulmonary tissue. Two general lines of endeavor have been pursued: an experimental study of the effects of these three substances on the lungs of dogs and rabbits[5,6] and a study of the routine autopsy material from stillborn and live-born infants. In the latter investigation, certain observations were made concerning the pathogenesis of the so-called vernix membrane and its possible relation to aspiration pneumonia in newborn infants which, it is believed, have not been considered by previous investigators. This report is concerned with the presentation of these observations and a discussion of their significance.

It has been generally believed that a "vernix membrane" is produced by the aspiration of vernix caseosa and the contents of the amniotic sac by the asphyxiated fetus and infant.[4, 7-10] The term "vernix membrane" was used first by Farber and Sweet[8] to describe the appearance of the material found plastered against the walls of the alveoli and bronchioles of the lungs of some newborn infants. Farber and Wilson[11] subsequently concluded that this type of membrane was identical in appearance and staining reactions with the hyaline membrane seen in the lungs of patients dying from the pandemic of

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influenza at the end of the first World War and from acute pneumonia of other etiologies. It was their opinion that, although the appearance of the two was similar, the pathogenesis of the "vernix membrane" was distinguished by the fact that it consisted of aspirated amniotic sac contents. The terminology adopted by Farber and Sweet was based upon the observation that the membrane contained cells that were apparently of the cornified epithelial type and fat, both of which are normal constituents of vernix. Their observations were made on infants born outside of the hospital, so that it was impossible to obtain accurate obstetric histories. Their material did not permit the correlation of the presence of the membrane with either the maturity of the infant or the time of death, nor did it include a routine estimate of the amount of fat and the numbers of apparently cornified epithelial cells in relation to the amount of "vernix membrane" or, as it shall be termed here, hyaline-like membrane and material in the lungs.

During the course of the present study, as a result of having taken the above factors into account, it became apparent that hyaline-like material (often in the form of a membrane) was frequently and almost exclusively found in the lungs of live-born premature infants and rarely in the lungs of stillborn or of live-born full term infants. The failure to identify the hyaline-like material in the lungs of stillborn infants, whose likelihood to aspirate as the result of asphyxia was greater than that of most of the live-born premature infants whose lungs contained this material, suggested that the aspiration theory might not be correct. This discrepancy between these postmortem findings and the currently held theory of "vernix membrane" formation has led to a reexamination of the facts on which the theory is based. From an appraisal of these facts it is suggested that the hyaline-like membrane or "vernix membrane" is not aspirated vernix but represents a tissue reaction to injury of the bronchioles, alveolar ducts and alveoli.

Material and Methods of Study

The autopsy files of the University of Kansas Medical Center were searched for the records of all stillbirths listed from 1941 to 1947 and all postmortem records on neonatal deaths from 1944 to 1947 inclusively. Stillbirths were excluded from this study only if the tissues were so badly macerated as to make the interpretation of the microscopic study of the lungs questionable, if the stillbirth occurred outside of this hospital, or if the mother's record was inadequate or could not be found. All neonatal deaths occurring in the first 30 days of life were accepted for study if the infant was born in this hospital with the exception of 3 obviously premature infants and 1 full term infant who were born on the outside but brought to this hospital for treatment. The birth weights of all the infants included in this study were accurately established with the exception of the 4 infants noted above and 1 stillborn fetus that was full term by all other standards. An additional group of 12 infants who had erythroblastosis fetalis and died in another hospital were also included in this study.*

The hospital records of the mothers and infants, the autopsy protocols and the microscopic sections of the lungs of all infants included in this study were examined. Estimates of the amount of vascular congestion, hemorrhage, edema fluid, pigment, exudation of mononuclear and polymorphonuclear leukocytes, accumulation of epithelial cells and so-called "vernix membrane" or free-lying "vernix" material was made on the lungs of each infant from the microscopic preparations made at the time of the original postmortem examination. All of the above sections had been stained with hematoxylin and eosin. In all instances in which blocks of lung tissues had been saved, sections were cut and stained with sudan III, so that the amount of fat could be estimated from a microscopic preparation. The amounts of the above constituents were graded on a scale of 0 to 4 plus. In addition, Masson, phosphotungstic-acid, hematoxylin stains and Perl tests were made on suitably cut sections of lungs of several infants.

* Dr. Russell Kerr and Dr. George Herrman of the staff of St. Joseph's Hospital, Kansas City, Mo., gave the authors permission to examine the hospital records and autopsy material on these infants.

Results

The recognition of the "vernix membrane" in the lungs of newborn infants offers no particular difficulty. In sections stained with hematoxylin and eosin it has a hyaline-like appearance and is a darker pink than either the red blood cells or serum sometimes seen in conjunction with it. The hyaline-like material is often plastered against the walls of the bronchioles or alveolar ducts but also can be seen lying loose in conglomerate masses within the alveoli (Fig. 1).

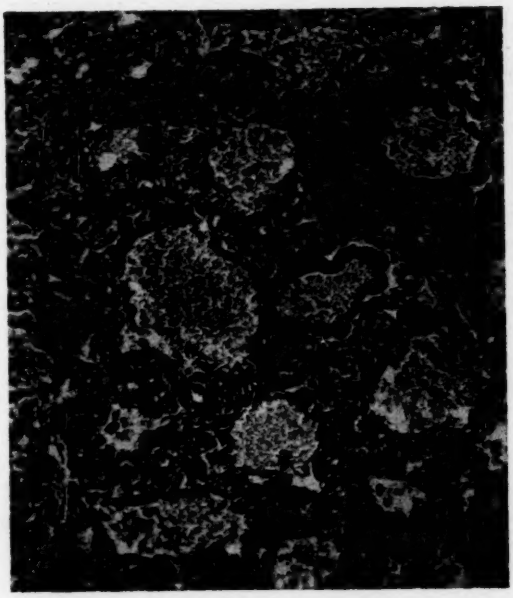

Fig. 1. Hyaline-like membrane in lung of newborn infant. (× 150)

A total of 79 infants, 32 stillborn and 47 live-born, on whom autopsies had been done in this hospital were included in this study. No hyaline-like material or membrane was seen in eight infants who survived more than 96 hours after birth (Table I). These eight infants were excluded from the group for which data are given in Table II concerning the distribution of hyaline-like material, fat and apparently cornified epithelial cells.

From the data in Table II it is seen that hyaline-like material was found in only 4 of the 32 stillborn infants as compared to 22 of the 39 live-born infants. The amount of hyaline-like material in the lungs of the stillborn infants exceeded a grade of 1 plus in only one of the four infants, while the data in Table III show that a grade of 1 plus was exceeded in 16 of the 22 live-born infants. In fact, 11 of the 22 live-born infants had a grade of 4 plus. The hyaline-like material in stillborn infants was never demonstrated in the form of a membrane plastered against the wall of air spaces.

The presence of hyaline-like material in the lungs appears to be definitely related to birth weight. Only one of the 17 infants, including stillborn and live-born, weighed

TABLE I

DISTRIBUTION OF HYALINE-LIKE MATERIAL IN LUNGS OF 47 LIVE-BORN INFANTS ACCORDING TO DAY OF DEATH

	Day of Death					Total
	1	2	3	4	5–10	
Autopsies with hyaline-like material	11	7	3	1	0	22
Autopsies without hyaline-like material	9	3	3	2	8	25
Total autopsies	20	10	6	3	8	47

TABLE II

DISTRIBUTION OF HYALINE-LIKE MATERIAL, CORNIFIED EPITHELIAL CELLS* AND FAT IN LUNGS OF 32 STILLBORN AND 39 LIVE-BORN INFANTS ACCORDING TO THEIR BIRTH WEIGHT

Birth weight kg.	Stillborn					Live-born				
	Total autopsies	with hyaline-like material	with fat		with cornified epithelial cells*	Total autopsies	with hyaline-like material	with fat		with cornified epithelial cells*
			stains done	stains positive				stains done	stains positive	
–1.0	0	0	0	0	0	8	2	5	0	1
1.0–1.5	7	1	4	0	0	6	5	5	0	4
1.5–2.0	4	1	1	0	1	6	6	6	0	1
2.0–2.5	6	1	3	2	2	4	2	4	1	1
2.5–3.0	3	0	1	0	2	10	7	10	4	2
3.0–	12	1	9	6	8	5	0	2	0	4
Total	32	4	18	8	13	39	22	32	5	13

* In this table cornified epithelial cells refer to the wavy-appearing cells which stain blue with hematoxylin and eosin.

TABLE III

AMOUNT OF HYALINE-LIKE MATERIAL IN LUNGS OF 34 LIVE-BORN INFANTS WEIGHING LESS THAN 3 KG. AT BIRTH AND DYING IN FIRST 4 DAYS OF LIFE ACCORDING TO BIRTH WEIGHT

Amount of hyaline-like material	Autopsies according to birth weight-kg.					
	–1	1–1½	1½–2	2–2½	2½–3	Total
0	6	1		2	3	12
1+	1	1			4	6
2+		1				1
3+	1	1	1	1		4
4+		2	5	1	3	11
Total	8	6	6	4	10	34

TABLE IV

DISTRIBUTION OF HYALINE-LIKE MATERIAL IN LUNGS OF 15 INFANTS DYING WITH ERYTHROBLASTOSIS FETALIS

	Stillborn	Live-born				Total
		Birth weight—kg.				
		1–2½	2½–3	3–	Total	
Total autopsies	2	2	5	6	13	15
Autopsies with hyaline-like material	0	2	4	0	6	6

over 3 kg. at birth and had hyaline-like material in the lungs, as shown in Table II. This stillborn infant weighed 3100 gm. at birth, and the hyaline-like material was graded as 1 plus. The great preponderance of positive findings was in the group of live-born infants who weighed between 1 and 3 kg. at birth. From the data in Table III it is clear that all of the premature infants who weighed between 1½ and 2 kg. at birth had positive findings, and also that the heaviest concentration of hyaline-like material was found in their lungs. Both the incidence and the amount of hyaline-like material tended to fall as the birth weight increased from this point.

At one time during the course of this study it was thought that infants dying with

FIG. 2. Bronchiole from same lung as Figure 1 showing (A) normal epithelium, (B) denuded area and (C) denuded area covered by hyaline-like membrane. (× 150)

erythroblastosis fetalis showed a higher incidence of hyaline-like material in their lungs than did other babies, but a study of the 15 unselected autopsies on such infants revealed that the incidence was not unlike that for other infants if the birth weight was taken into account. The data on this small and special group of 15 infants have been presented in Table IV, since they confirm the results reported in Tables II and III, indicating the importance of the immaturity of the infant, as judged by birth weight, in respect to the presence of hyaline-like material in the lungs.

There were 54 infants whose blocks of lung tissue were available for fat stains. Four of the 54 infants survived more than four days and were excluded from consideration

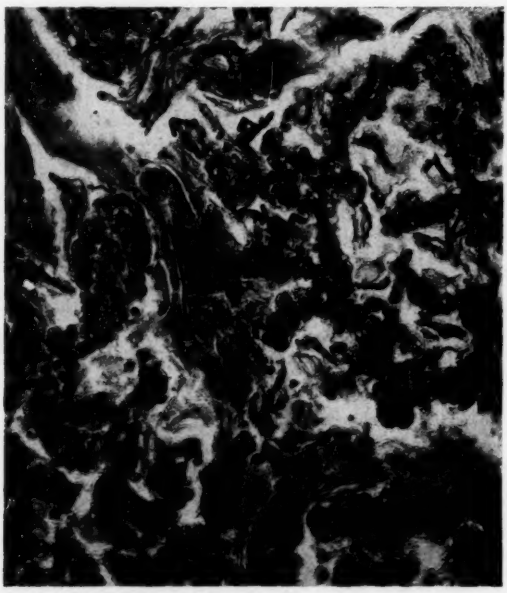

FIG. 3. Masses of wavy, cornified, blue-staining epithelial cells in lung of stillborn infant. (× 150)

in Table II. One of the four who was excluded had fat in the lungs, but it was not associated with hyaline-like material or cornified epithelial cells. The distribution of positive fat stains on the lungs of the remaining 50 infants is given in Table II. The incidence of positive fat stains was the opposite of the distribution of hyaline-like material, both in respect to the time of death and birth weight. Fat was found in the lungs of 8 of the 18 stillborn infants and in only 5 of the 32 live-born infants. Ten of the 13 infants, both stillborn and live-born, with positive fat stains weighed more than 2.5 kg. at birth. The only group of infants in which there appeared to be any significant relationship between the presence of fat and hyaline-like material was the group of full term infants weighing between 2½ and 3 kg. at birth. In this more mature group the fat definitely could be seen as a membrane, presumably a part of the hyaline-like membrane, lining the walls of the alveolar ducts and bronchioles. The notable absence of fat, however, from the hyaline-like membranes seen in the relatively large group of

premature infants' lungs suggests that some factor other than the aspiration of vernix was operating to produce this clear-cut discrepancy between the premature and full term infants.

The highest incidence of positive fat stains was found among the stillborn infants with birth weights in excess of 3 kg. In the lungs of these infants the fat did not appear in the form of a membrane lining the alveolar ducts or bronchioles, but was lying in a diffuse manner within the lumen of the alveoli. It is interesting that, of this group, there was a large number whose lungs also contained what appeared to be cornified epithelial cells as well as fat.

The significance of the presence of what are thought to be cornified epithelial cells derived from the skin and present in large numbers in meconium, vernix and amniotic fluid is deferred for the present and will be discussed in relation to the development of

FIG. 4. Masses of cornified epithelial cells in alveoli, dilated air spaces without membrane formation in spite of heavy fat deposits in alveoli of same lung as Figure 3. (× 70)

the hyaline-like membrane. It is sufficient to indicate here that the data in Table II refer to epithelial cells that have a wavy appearance and stain blue with hematoxylin and eosin and are to be distinguished from cells which are epithelial in appearance and also are seen within the alveoli, but are flat and stain from a dark to a light pink.

If the theory of aspiration were correct, it would be expected that those infants whose mothers' pregnancies and labors were complicated, particularly by sudden and accidental interruption of blood flow through the placenta and the umbilical vessels, would be most likely to have "vernix membranes" or hyaline-like material in their lungs from gasping. There were 14 pregnancies in this study that were complicated by either a placenta previa, premature separation of the placenta or prolapse of the cord, and hyaline-

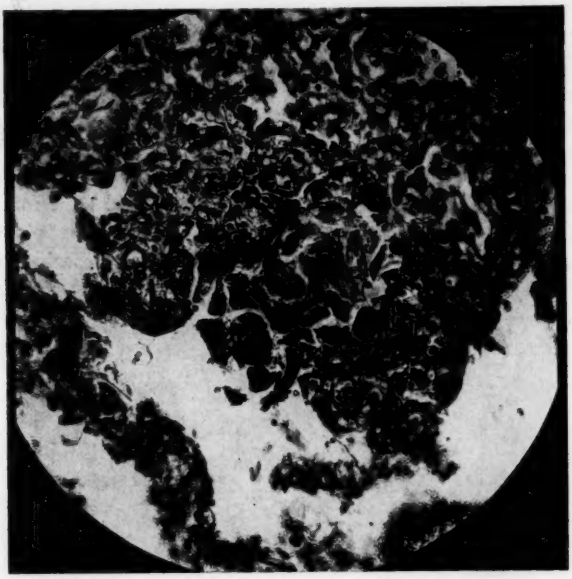

FIG. 5. (A) Conglomerate mass of large, flat, pink-staining cells in terminal air space. Fat stain negative. (B) Hyaline-like membrane present. (× 320)

FIG. 6. (A) Hyaline-like material surrounded by (B) polymorphonuclear leukocytes and small mononuclear cells in terminal air space. (× 320)

like material was found in only three of the infants' lungs. In none of the three infants did the hyaline-like material amount to more than a grade of 2 plus. In the group of premature live-born infants in which both the amount and incidence of hyaline-like material were highest, i.e., the group with birth weights between 1 and 2½ kg., there were 11 infants whose mothers' pregnancies and labors were uncomplicated except in one instance by twins and in another by diabetes. However, 9 of the 11 infants had hyaline-like material in their lungs and in no instance was it graded less than 3 plus. One of the nine infants had erythroblastosis fetalis and another died with sclerema. In the remaining seven infants the autopsies were not remarkable except for the presence of the hyaline-like material in the lungs. The absence of other significant findings in the autopsies of these premature infants suggested that the extensive hyaline-like membranes might have been a principal cause of their deaths.

Microscopic studies of the lungs containing hyaline-like membranes show that many of the bronchioles and alveolar ducts were denuded of epithelium. In most instances the denuded areas were covered with the hyaline-like material, but there were many bronchioles, such as is shown in Fig. 2, in which there were denuded areas lying between normal epithelium on one side and membrane on the other, suggesting a transition zone between the uninjured and membrane-covered parts. Repeated and extensive search failed to show hyaline-like membranes overlying intact epithelium of the bronchioles and alveolar ducts. The extent of membrane formation appeared to be directly proportional to the amount of epithelium lost. Congestion of the pulmonary vessels, interstitial edema, protein precipitate in the alveoli, and hemorrhages in the alveoli and bronchi were frequently found associated with membrane formation, although there were instances in which the membranes were found in the absence of congestion, edema or hemorrhage.

The sections of lungs of some fetuses contained massive collections of wavy, flattened, compressed, blue-staining structures, presumably cornified epithelial cells shed from the skin of the fetus and aspirated into the terminal air spaces. A typical example from a stillborn fetus that weighed 3500 gm. is shown in Fig. 3. In this particular case the number of epithelial cells and the amount of fat were each graded 4 plus. Although the air spaces were markedly distended in this case, as shown in Fig. 4, no hyaline-like membranes were observed in any of the sections made. (The mechanism by which the air spaces became distended in this case and in some of the other stillborn infants is not understood, but it was not an infrequent observation even though death had occurred several hours before delivery.) In spite of the fact that there were considerable amounts of cornified epithelial cells present in the alveoli in this case, as shown in Figs. 3 and 4, and in spite of the fact that fat was abundant in the alveoli, the cornified epithelial cells stained blue and not pink. According to the theory of Farber and Sweet[8] it would be expected that some of the cornified epithelial cells would stain pink with an H and E stain as the result of being coated with fat. Furthermore, when the large pink-staining cells described by Farber and Sweet were seen, as shown in Fig. 5, the fat stains were negative in almost all cases. Fig. 5 is a photomicrograph of a section of lung of a premature infant who weighed 1685 gm. at birth and died at 28 hours of age. The fat stain on the lung of this infant was negative. It is noted that these large pink-staining cells in Fig. 5 are mostly anuclear and flat. The stain varies from a pink to a lemon yellow color and small yellow-brown granules can be seen in some of them in considerable amounts. In Fig. 5 the large collection of pink-staining cells in the center is contiguous with a hyaline-like membrane on the left.

The presence of polymorphonuclear leukocytic exudate in the bronchi and alveoli was observed chiefly in live-born premature infants with hyaline-like membranes and in full term stillborn infants with large amounts of fat and numbers of what appeared to be cornified epithelial cells in their lungs. There were six live-born infants whose lungs showed hyaline-like material and phagocytes in the terminal air spaces and five of the six infants weighed less than 2.5 kg. at birth. An example of the close relationship between the hyaline-like material and the cellular exudate is shown in Fig. 6. Characteristically, the polymorphonuclear leukocytes and the monocytes are congregated about the hyaline-like material. These six infants survived from 7 to 84 hours after birth and three of them died 58 hours or more following delivery. There were four live-born infants with polymorphonuclear cells present among the 25 live-born infants who did not have hyaline-like material in their lungs. The only other cases of pneumonia were found in four full term stillborn infants, none of which had hyaline-like material present.

Discussion

Hyaline-like membranes were found in the lungs of almost 50% of the live-born infants in the present study and their presence may have been the leading cause of death in several of them. Consequently it is important that the pathogenesis of these membranes be as completely understood as possible. In the present study the previously held theory of the formation of these membranes from aspiration of amniotic sac contents has been set aside and in its place the concept has been developed that these membranes are the result of an injury to the lung, the nature of which is not apparent at the present time. A good deal of the argument against the aspiration theory hinges on the answers to these two questions: What infants are most likely to aspirate and what are the evidences of aspirated amniotic sac contents?

The answer to the first of these questions has been sought by previous investigators through animal experimentation and studies on the human fetus. While there is considerable debate as to whether or not amniotic fluid can enter the terminal air spaces under the usual conditions prevailing during fetal existence, there is general agreement that suddenly induced anoxia, such as is produced by clamping the umbilical cord, frequently causes the fetus to make gasping respiratory efforts.[12–16] Such efforts can result in the entrance into the most distal portions of the lung of whatever fluid surrounds the fetus. Besides anoxia, the age of the fetus apparently is a factor in aspiration, as suggested by the postmortem studies of Wilson and Farber[17] on the lungs of 100 full term infants and of more than 200 premature infants. They concluded that the aspiration of amniotic sac contents was not so important a problem in premature infants as in full term infants, and pointed out that there were smaller amounts of vernix and a smaller number of cornified cells in the sac contents of premature infants, since the cornification of the skin of the fetus and the production of vernix take place largely in the last months of pregnancy. On the basis of these observations it would be expected that stillborn full term infants would be most likely to aspirate amniotic sac contents and that live-born premature infants would be least likely.

Less attention has been given to the problem of what constitutes acceptable evidence of aspirated amniotic sac contents. The presence of cornified epithelial cells that stain blue has been universally accepted as evidence of aspiration. However, since such cells appear in amniotic fluid, vernix and meconium, it is impossible to tell whether one or all three have been aspirated from a study of these cells alone. They can be found in

varying quantities in the lungs of almost all fetuses and of many newborn infants. Fat is present in both meconium and vernix. It can be found in the alveoli of some fetuses, but there is no method at present for determining whether it is derived from the amniotic sac contents or from the fetal circulation as the result of a possible injury to the capillary bed of the lungs. If it is assumed that the combination of relatively large numbers of cornified blue-staining epithelial cells plus large amounts of fat in the air spaces represents either aspirated vernix or meconium, then the results of the present study indicate that the group of full term stillborn fetuses is the one most likely to aspirate these materials. The combination of large amounts of fat plus large numbers of cornified epithelial cells was not encountered in the lungs of any of the live-born infants. The fact that hyaline-like membranes were almost exclusively observed in premature live-born infants, the group which by theory and observation is least likely to aspirate amniotic sac contents, makes it seem unlikely that aspiration produced them.

Although it appears that the hyaline-like membrane in the lungs of newborn infants may not be derived from vernix, it is difficult to be certain of the pathogenesis of this lesion. Farber and Wilson[11] have pointed out the similar appearance of the membranes in the lungs of newborn infants and those in older individuals who either died during the pandemic of influenza or succumbed to acute pneumonia of other etiologies. The resemblance between the lesions in newborn infants and those in individuals who died with rheumatic pneumonia and the membranes produced experimentally in dogs by the inhalation of cadmium chloride is equally good.[18, 19] There seems to be no agreement, however, as to how these membranes are formed. The various theories have been reviewed by Farber and Wilson, who concluded that the formation of the membrane was dependent neither on necrosis of the walls of the terminal air spaces nor on vascular damage. It was their belief that in older individuals the membrane consisted in necrotic cells and exudate displaced toward the periphery of the terminal air spaces by forcefully inspired air; in newborn infants vernix was present in place of exudate. They attempted to reproduce these membranes by introducing exudate and other substances (not vernix) into the lungs of experimental animals and then forcing them to overbreathe.[20] While these experiments resulted in membranes lining the alveoli and alveolar ducts, they differed from those seen in humans in that the fat stains of sections of lung were negative in all animals. In this study, experiments on 29 dogs and rabbits were unsuccessful in producing hyaline-like material or membranes in the lungs by the intratracheal instillation of vernix, meconium or amniotic fluid.

The results of the present study suggest that the hyaline-like membranes in the lungs of newborn infants are due to injuries, probably sustained during fetal life, involving the epithelium of the terminal air spaces and also probably involving the vascular bed of the lungs. It remains to be determined whether the etiologic agent is an infection, as so often seen in older individuals, or some other agent. The fact that the hyaline-like membranes are seen exclusively in live-born infants does not preclude the possibility that the injury could have occurred during fetal existence. An injury to the terminal air spaces of the fetus would not necessarily be lethal while the fetal and placental circulations were intact, but as soon as the organism became dependent on pulmonary respiration, the effects of such an injury would make themselves manifest if any large portion of the lung were involved. It is clear that whatever the injurious agent may be it is not related to obvious maternal complications of pregnancy or labor, since in the majority of cases there were no complications except the premature onset of labor.

The fact that fat was demonstrated in the hyaline-like membranes of many live-born infants whose birth weights were over 2.5 kg. and rarely in those who weighed less than 2.5 kg. at birth suggests that the appearance of fat in the lesion may have been related to the age of the lesion. From the point of view of pathogenesis it would be interesting to determine whether or not fat appeared late in the course of similar lesions in older individuals, the onset of whose illness could be determined with some accuracy.

The derivation of the large pink-staining cells, which appear to be intimately associated with the hyaline-like membranes and seem to form a part of the membrane, needs further study. The present investigation suggests that these cells may be fibroblasts or distorted macrophages and are not cornified epithelial cells shed from the infant's skin and covered with fat. Study of the lungs of older children in the autopsy material indicates that similarly appearing cells are to be found in the lungs containing hyaline-like membranes, although not to the same extent as seen in the newborn infant.

The relationship of hyaline-like membranes in the lungs of newborn infants to atelectasis and its attendant symptoms is obvious and is described in some pediatric textbooks.[9,10] The possible association of these lesions with pneumonia in the newborn has not been considered. As for the hyaline-like material in the lungs of older individuals, Wohlbach[21] concluded from microscopic studies that this material was phagocytized by polymorphonuclear leukocytes and mononuclear cells. Similar impressions were gained in the present study in 6 of the 14 cases of pneumonia characterized by large numbers of phagocytes in the alveoli and bronchi. All six cases were found in live-born infants. The impression was also obtained that aspiration of amniotic sac contents per se could produce pneumonia, but evidence for this opinion was found only among full term stillborn infants in which the lungs contained the greatest amounts of fat and blue-staining epithelial cells. Pneumonia was not found in stillborn infants except when large amounts of fat were present and usually it occurred only if fat and cornified epithelial cells were found together. Experimental studies with animals suggested that either sterile meconium, vernix or amniotic fluid is capable of producing a polymorphonuclear exudate within a few hours of their introduction into the lungs, but species differences in the amount of polymorphonuclear cell response introduce a word of caution in concluding that the effect of these materials on the human lung is just the result of chemical irritation.[6] The role of infection cannot be minimized. However, instead of thinking of pneumonia in the newborn only in terms of infection or chemical irritation of aspirated material, there is suggestive evidence that some cases of pneumonia occur as the result of the production of hyaline-like material in the terminal air spaces.

This material has been reviewed in the light of the observations on congenital alveolar dysplasia made by MacMahon,[22,23] who used this term to designate arrested alveolar development of unknown etiology with consequent reduction in numbers of alveoli and a relative thickening of the alveolar walls with mesenchymal tissue. Interest was aroused by the membranes present in some of his microscopic preparations which were referred to as "fibrinoid exudate." From his description, the fibrinoid exudate would seem to be identical with the hyaline-like membranes discussed in the present study. In the latter the development of the alveoli in the group whose birth weights were less than 2500 gm. and whose lungs contained hyaline-like membranes was essentially as would be expected for infants of their degree of immaturity. Among the infants over 2500 gm. who had hyaline-like membranes in their lungs the estimate of the degree of alveolar development was equivocal because the presence of mononuclear cells and

edema in the parenchyma of the lung associated with varying degrees of polymorphonuclear leukocytes in the alveolar spaces precluded an accurate estimate of the number of alveoli. When pneumonitis was present in this series, the possibility of alveolar dysplasia was accentuated, but it was not certain that this picture of dysplasia was not more apparent than real. MacMahon stated, "At first glance under the microscope the lesion suggests a non-specific, proliferative, interstitial pneumonitis . . . ," but in the absence of signs of inflammatory disease he interpreted the histologic pattern as representing the immature lung.[22] The microscopic appearances of the lesions described by MacMahon and in this study have a considerable similarity. The fact that the etiology of the lesions in both studies remains in doubt and the fact that MacMahon's reports included but three cases indicate the need for further study to determine whether or not the pathogenesis of the lesions described in these two studies have any ground in common.

Summary

The clinical records of 79 stillborn and live-born infants were correlated with the postmortem findings in their lungs.

Evidence of aspiration was found chiefly in the lungs of full term stillborn infants in the form of large numbers of blue-staining cornified epithelial cells together with large amounts of fat in the terminal air spaces.

Hyaline-like membranes were found in the terminal air spaces in greatest numbers in the lungs of live-born premature infants in whom there was no history of any maternal complication of pregnancy or labor.

It is suggested that the hyaline-like membranes may not be composed of aspirated vernix and amniotic sac contents but probably represent a reaction to an injury to the epithelium of the air spaces, especially the bronchioles and alveolar ducts.

The nature of the etiologic agent remains doubtful, but the similarity of these membranes to those found in older individuals dying of pandemic influenza and with rheumatic pneumonitis suggests that intrauterine inflammatory reaction may be a factor. The relationship to congenital alveolar dysplasia has been discussed.

It is suggested that the hyaline-like material is phagocytized by polymorphonuclear leukocytes and mononuclear cells. The presence of these phagocytes in the alveoli and bronchi in association with hyaline-like material is one of the chief forms of pneumonia in the newborn infant.

Acknowledgment

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SPANISH ABSTRACT

Patogénisis de la Membrana Vernix; Relación a la Neumonía por Aspiración en los partos muertos y en los infantes recien-nacidos

Los datos clínicos de 79 infantes nacidos muertos y vivos fueron puestos en correlación con los descubrimientos postmortem en sus pulmones.

La evidencia de aspiración se encontró principalmente en los pulmones de niños nacidos muertos, de término completo, en la forma de gran número de células epiteliales cornificadas de coloración azul junto con grandes cantidades de grasa en los extremos de los espacios de aire.

En los pulmones de los infantes prematuros que nacieron vivos, y sobre quienes no se tenía ningún precedente de complicación maternal durante el embarazo o el parto, se encontraron membranas hialinas en el extremo de los espacios de aire en gran número.

Se ha sugerido que las membranas hialinas no están compuestas de vernix aspirado ni del contenido del saco amniótico sino que probablemente representa una reacción a un daño hecho al epitelio de los espacios de aire, especialmente los conductos bronquiales y alveolares.

La naturaleza del agente etiológico permanece dudoso, pero la similaridad de estas membranas a aquellas que se han encontrado en individuos mayores muriendoso de influenza pandémica y con neumonitis reumática sugiere que la reacción inflamatoria intrauterina pueda constituir un factor. Se ha tratado de la relación con la displasia alveolar congénita.

Se ha sugerido que la materia hialina está fagocitada por leucocitos polimorfonucleares y células mononucleares. La presencia de estos fagocitos en los alvéolos y bronquios en asociación con la materia hialina es una de las principales formas de neumonía en el infante recién-nacido.

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PANCREATIC ENZYMES: NORMAL OUTPUT AND COMPARISON OF DIFFERENT METHODS OF ASSAY

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THE IMPORTANCE of the digestive function of the pancreas has been known since the earliest days of clinical medicine and it has also been long realized that an estimation of the ferments in the duodenal juice would yield much more useful information on excretory function of the pancreas than their determination in the feces. There was, however, no reliable way of collecting fluid from the duodenum until Einhorn[1] in 1910 devised his tube. It was then only a year until Hess[2-4] developed his tube for infants and published the first pediatric reports on enzymic activity. Since then many different methods have been devised for the estimation of the three pancreatic enzymes.

There is, however, a consistent difficulty in evaluating and comparing the findings of the different authors because only a few of them have used the same methods of estimation and every method yields different figures for the same enzymic values. Moreover, the values various authors give to the same, the so-called normal ranges, or to the lowest limits of these, differ more widely than in any other field of medicine. To quote an example, Wohlgemuth,[5] working with his own method, found amylase values between 625 and 2500 for normal and the same figures were given by Simon.[6] At the same time, Kitaigorodskaja,[7] using the same estimation, gives a range of as low as 17-200. The situation is quite the same for the other two enzymes, trypsin and lipase.

Equally diverging are the opinions of the different authors on a number of other questions, such as the enzymic level of the same subject at different times and following different diets, the rate of flow and a possible parallelism in the output of the different enzymes.

It seemed, therefore, useful to make parallel observations using different methods of assay on a group of healthy children both for the sake of studying normal conditions and in order to establish a common denominator which would, independently of the method of estimation used and of the enzyme in question, indicate the normal or pathologic character of the findings.

METHODS

Collection of Fluid: For the examinations, the duodenal contents were collected after a fasting period of 6 to 12 hrs. The older the child, the longer was he deprived of food. All subjects were encouraged to drink water up to 1 hr. before examination. A simple Einhorn tube with a lumen of 2 mm., bearing a metal tip 4 mm. in diameter and markings at every 5 cm., was used. After an approximate estimation of the distances from the mouth to the cardia and from the cardia to the Vater's papilla and the duodenojejunal flexure, the tube was passed through the nose or the mouth. The contents of the stomach were aspirated with a syringe and then the child was placed on his right side with slightly elevated hips and the tube allowed to enter the duodenum. Its position was ascertained by fluoroscopic control. When the tip passed the pylorus, a second tube of the same pattern as the first one was introduced into the stomach and left in place throughout the whole examination to aspirate the gastric secretion and the saliva swallowed. The duodenal fluid was from time to time

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collected by a syringe attached to the tube. Time and amounts were carefully recorded and the specimens kept on ice until the examination which always took place within an hour. (There were cases in which the output and activity of enzymes were determined also after stimulation with either ether or secretin. The results of these observations will not be presented in this article but will be dealt with elsewhere.)

Analysis of Duodenal Contents was made by the following methods:

1. *Amylase:* Wohlgemuth's[8] iodometric determination was carried out using a 1% solution of Merck's starch. To avoid a change in the final color, iodine was added in form of 5 ml. of 1:500 N. solution containing some drops of acetic acid.[8] Two or three parallel rows, each containing 13 test tubes were set up with amounts of 1.0 to 0.00025 ml. of enzyme solution. In order to obtain more precise values, in many instances a second determination was made with 8 tubes containing dilutions between those in the tubes right and left from the end point of the first series.

Ågren and Lagerlöf's[9] method was used in its original form. Equal parts of Sørensen's phosphate solutions were used for stabilization.

2. *Trypsin:* The Michaelis[10] method was carried out by using freshly prepared solutions obtained by dissolving 0.10 gm. pure casein in 11 ml. of 0.1% solution of sodium bicarbonate, to which a drop of chloroform was added. Thirteen test tubes, containing amounts of 1.0 to 0.00025 ml. of enzyme solution, were used. In several cases, also, further determinations were made with dilutions on both sides of the first end point.

Ågren and Lagerlöf's[9] assay of trypsin was made as originally described, but digestion was carried out at 38°C. instead of 30°C.

Fermi's method was used in the modification of Andersen and Early.[11]

3. *Lipase:* In Willstätter's[12] titrimetric method, a standard olive oil with a saponification number of 185.5 was used. A lipase unit, therefore, would equal 19.8 ml. of a tenth normal solution of potassium hydroxide. The reaction was terminated by addition of a mixture of alcohol and ether 3:1. Thymol blue was used as an indicator.

Rona and Michaelis'[13] stalagmometric method was used both in its original form and in the modification of Willstätter and others.[14] Ammoniacal buffers were used for stabilization and albumin, sodium oleate and calcium chloride for activation.

Leubner's[15] photometric triolein method and Freudenberg's[16] titrimetric method were used according to the original descriptions. All determinations were made in duplicate or triplicate.

Material

Forty-seven normal and healthy children, 21 male and 26 female, were examined. Their ages, recorded in Table I, varied from 11 months to 10½ years. They were not considered normal unless they were above the height and weight standards of their respective age groups. All were free of complaints, and showed a negative response to intradermal tuberculin, and gave negative complement fixation tests for syphilis. All had a good appetite and had no digestion anomalies.

Observations

In 20 children the different samples yielded by single tubings were not examined separately but mixed and the enzymes determined in an aliquot part of the total amount. In 11 children this same procedure was repeated on different days. In 16 children each sample obtained by aspiration every 10 minutes for 30 to 90 minutes was examined separately; in nine of them this observation was undertaken on two or more occasions within one to four weeks.

1. *Amylase:* 167 determinations were made with Wohlgemuth's and 121 with Ågren and Lagerlöf's method. The results are presented in Table I.

In Table I, the values of the first method refer to ml. of starch solution digested by 1 ml. of duodenal juice in 30 minutes, while those in the second column refer to hundredths of grams of maltose liberated by 1 ml. of enzyme solution in 10 minutes, i.e. to hundredths of Ågren-Lagerlöf units.

TABLE I.—AMYLASE DETERMINATIONS

No.	Sex	Age Yr.	Age Mo.	Days later	Wohlgemuth (units) minutes 0 10 20 30 40 50 60 70 80	Agren and Lagerlöf (units/100) minutes 0 10 20 30 40 50 60 70 80
1	M	—	11		256	45
2	F	—	11		640– 384– 384–448–640–512	115– 70– 68– ?–120– 90
2a				2	512	
2b				5	640– 512	120– 85
2c				9	448– 384– 512–512–512–256–320–384	78– 68– 90– 89– 88– 46– ?– 70
3	F	1	—		512– 448– 224–512–448	88– 79– ?– 37– ?– 83
3a				1	896– 512–	170– 90–
3b				2	640– 896–	120–170–
3c				4	512–1536–	98–200–
4	M	1	—		1024–	166–
5	M	1	1		256–	46–
6	F	1	6		448– 448– 512–384–448–	
6a				3	896–1536–	
6b				14	512– 256– 224–320–512–512	
6c				15	224– 640–1024–512–	
6d				21	448–	
7	F	1	6		2048–	196–
7a				1	896–	150–
7b				3	512–	90–
8	F	1	7			51
9	M	1	11		896–1024–2048	170–168–245–
9a				3	640– 768– 448–448–512–	120–140– 80– 85– 86–
9b				16	512– 256– 384–768–320	96– 48– 70–100–165– 47–
10	M	2	—		192–	37–
11	F	2	1		512–	90–
11a				1	192–	34–
11b				9	512–	82–
11c				20	448–	77–
12	F	2	2		512–	
13	M	2	6		448– 192– 256–192–448–640–512–	
14	M	2	8		512–	81–
14a				1	224–	?–
14b				4	256–	44–
15	F	3	1		448–	80–
15a				3	640–	?–
15b				7	1024–	146–
15c				13	640–	108–
16	F	3	1			56–
17	M	3	4		192–	
17a				1	256–	
18	M	3	4		224–	
18a				3	512– 256– 192–160–320–256–224–320–384–	
19	F	3	8		1024–	100–
20	M	3	10		256– 224– 448–640–512–384–	47– 40– 72–120–101– 72–
21	F	3	10		448–	81–
21a				2	192–	34–
21b				20	384–	70–
22	M	4	1		512–	
23	F	4	2			115– 56– 37– 45– 39–
23a				3		56– 35–
23b				9		85– 62– 48– 45– 90–115– 80–
24	F	4	2		448– 640– 320–320–384–	76–121– 62– 66– 80–
25	M	4	5		512– 256– 512–	
26	F	4	5		224–	45–
26a				3	160–	33–
26b				8	512–	116–
26c				17	256–	56–
27	M	4	6		1024–	
28	F	5	1		1024–	182–
28a				4	512– 256– 512–512–	97– 60– 91–100–
29	M	5	3			163–
30	F	5	8			77–
31	F	5	10		768–	90–

TABLE I—*Continued*

No.	Sex	Age Yr.	Age Mo.	Days later	Wohlgemuth (units) minutes 0	10	20	30	40	50	60	70	80	Agren and Lagerlöf (units/100) minutes 0	10	20	30	40	50	60	70	80
32	F	6	3											100–								
32a				1										61–								
33	M	6	6		256–	256–	512–															
34	F	6	7		512–																	
35	M	6	11		256–	192–	256–															
35a				7	512–	512–	256–	256–	256–													
36	F	7	3		1024–									160–								
36a				14	512–									120–								
37	F	7	6		256–									56–								
38	F	7	10		768–	1024–	512–	512–														
39	M	8	—		1536–									182–								
39a				2	512–	640–	256–	256–	320–					101–	102–	62–	59–					
39b				7	512–	1024–	512–							105–	165–	80–						
40	F	8	2											72–								
41	F	8	9		320–									72–								
42	M	8	11		448–																	
43	M	9	3		192–																	
43a				7	256–																	
43b				17	512–																	
44	F	9	7		192–	256–	224–	512–	224–					40–	44–	44–	100–	60–				
45	M	10	—											56–								
46	F	10	—											140–								
47	M	10	5		448–									66–	116–							
47a				1	224–									50–								
					n=167									n=122								
					mean=498.2±21.9									mean= 89.3±3.8								
					S.D.=284									S.D.= 41.4								
					Coeff. of Var.= 56.8%									Coeff. of Var.= 36%								

TABLE II

CHARACTERISTIC VALUES OF DIFFERENT METHODS

		Amylase		Trypsin			Lipase		
		Wohlgemuth units	Ågren-Lagerlöf units	Michaelis units	Ågren-Lagerlöf units	Fermi-Andersen No. of tube	Willstätter units	Leubner per cent	Freudenberg units
Highest value recorded		2048	2.45	1024	3.5	2	53	72	8.5
Normal range	Upper Limit	1024	1.70	1024	3.2	3	45	60	7.5
	+S.D.	896	1.30	768	3.0	3	35	50	6.6
	Mean	512	0.89	448	2.2	4	26	35	5.3
	−S.D.	256	0.48	256	1.4	5	18	20	4.0
	Lower Limit	192	0.34	160	0.8	5	16	10	3.5
Lowest value recorded		160	0.33	128	0.8	6	13	8	3.0

TABLE III. TRYPSIN DETERMINATIONS

No.	Michaelis (dilution units) minutes									Ågren and Lagerlöf (in 0.1 ml. of n/10 NaCH) minutes										Andersen (serial No. of tubes) minutes				
	0	10	20	30	40	50	60	70	80	0	10	20	30	40	50	60	70	80	90	0	20	40	60	80
1	224									20										5				
2	512–	512–	256–	256–	384–	320				40–	38–	25–	28–	29–	30									
2a	448									33														
2b	512–	320								36–	29													
2c	384–	384–	512–	640–	768–	224–	224–	224		31–	34–	39–	48–	57–	40–	38–	30							
3	320–	320–	256–	512–	640–	320				28–	26–	21–	36–	46–	27									
3a	512–	?								38–	30													
3b	448–	512								27–	34–													
3c	640–	512–								42–	36													
4	640									47														
5	448									31										4				
6	320–	448–	512–	512–	256–					25–	32–	37–	40–	24						4–	4–	3–	3–	5
6a	512–	320–								35–	27–									3–	4–			
6b	384–	384–	192–	192–	160–	192–	224			28–	26–	18–	17–	18–	22–	23–				4–	4–	5–	6–	5–
6c	160–	384–	640–	512–						21–	28–	47–	41–							5–	4–	3–	3–	
6d	320–									25–										4–				
7	1024–									52–										3–				
7a	512–									37–										3–				
7b	448–									34–										4–				
8	320–									26–										4–				
9	512–	768–	1024–							36–	51–	66–								3–	3–	2–		
9a	640–	384–	384–	320–	320–					41–	29–	28–	26–	23–						3–	4–	4–	4–	5–
9b	320–	160–	160–	384–	512–	512–				26–	19–	21–	27–	36–	38–					4–	5–	5–	4–	4–
10	160–									20–										5–				
11	128–									17–										6–				
11a	160–									19–										6–				
11b	384–									26–										4–				
11c	384–									28–										4–				
12	320–																							
13	640–	256–	192–	128–	320–	768–	512–																	
14	320–									27–														
14a	224–									23–														
14b	192–									21–														
15	320–									29–										4–				
15a	384–									36–										4–				
15b	384–									38–										4–				
15c	512–									55–										3–				
16										50–										3–				
17										21–										5–				
17a										29–										4–				
18										28–										4–				
18a										35–	27–	21–	18–	32–	30–	20–	20–	25–	36–	4–	4–	4–	5–	4–
19	768–									63–														
20	192–	192–	256–	512–	512–	256–				21–	22–	27–	34–	35–	20–									
21	320–									32–										4–				
21a	640–									58–										3–				
21b	512–									49–										3–				
22	448–																			4–				
23										60–	32–	27–	27–	36–						3–	4–	4–	4–	4–
23a										42–	33–									3–	4–			
23b										50–	41–	39–	37–	51–	57–	47–				3–	4–	4–	4–	3–
24	256–	1024–	256–	192–	256–					29–	55–	31–	26–	33–										
25	512–	192–	384–																					
26	640–									57–														
26a	256–									28–														
26b	512–									51–														
26c	384–									37–														
27	512–																							
28	512–									42–										3–				
28a	320–	224–	224–	224–						30–	26–	24–	26–							4–	4–	5–	4–	
29										60–										3–				
30										18–										6–				
31	512–									57–										3–				

TABLE III—*Continued*

No.	Michaelis (dilution units) minutes									Ågren and Lagerlöf (in 0.1 ml. of n/10 NaCH) minutes										Andersen (serial No. of tubes) minutes				
	0	10	20	30	40	50	60	70	80	0	10	20	30	40	50	60	70	80	90	0	20	40	60	80
32										59–										3–				
32a										50–										3–				
33	224–	448–	640–							21–36–56–										5–	4–	3–		
34	320–									29–										4–				
35	192–	128–	192–							21–16–23–										5–	6–	5–		
35a	320–	192–	160–128–128–							34–20–16–15–16–										4–	5–	6–	5–	6–
36	896–									68–														
36a	512–									37–														
37	224–									26–										4–				
38	384–	256–	512–256–							31–25–54–30–										4–	4–	3–	4–	
39	1024–									70–										2–				
39a	448–	384–	320–256–320–							39–34–30–26–27–										3–	4–	4–	4–	4–
39b	512–	512–	256–							50–48–26–										3–	3–	4–		
40										62–										3–				
41	256–									27–										4–				
42	384–									39–										3–				
43	160–									18–										6–				
43a	224–									23–										4–				
43b	448–									41–										3–				
44	192–	192–	320–448–384–							21–20–33–45–37–										5–	5–	4–	3–	3–
45										29–										4–				
46										38–										3–				
47	320–	512–	896–							33–58–67–										4–	3–	2–		
47a	224–									22–										5–				
	n = 160 mean = 447 ± 15 S.D. = 193 C. of V. = 43									n = 183 mean = 44 ± 1.2 S.D. = 16 C. of V. = 43										n = 133 mean = 3.96 ± 0.08 S.D. = 0.94 C. of V. = 27				

The mean was found to be 498.2 ± 21.9 and rounded off to the nearest tube, 512, Wohlgemuth and 0.89 ± 0.03 Ågren-Lagerlöf units. (Characteristic values of all the methods are summarized in Table II.) Both methods were found serviceable and parallel estimations corresponded well in each of them. The advantage of the first one is its simplicity, whereas, the second gave more uniform results.

2. *Trypsin:* 160 estimations were made with Michaelis' method, 183 with Ågren and Lagerlöf's and 133 with the Fermi-Andersen method. Results are tabulated in Table III.

In Table III, values in the first column refer to digestion with 1 ml. of enzyme solution for 60 minutes; those yielded by the second method indicate twentieth units, i.e. 0.1 ml. of a tenth normal solution of sodium hydroxide necessary for titration after 20 minutes' incubation; and those in the third, serial numbers of test tubes of which No. 2 contained 0.0025 ml. of duodenal juice; No. 3, 0.005 ml., No. 4, 0.01 ml., etc. Digestion lasted an hour.

The mean for the Michaelis' method was found to be 447 ± 15 and this was rounded off to 448, for the Ågren-Lagerlöf method 44·0.1 ml. ± 1.2; i.e., 2.2 ± 0.1 units, and for the Fermi-Andersen method 4 ± 0.1. (Other values are given in Table II.) As can be seen from the parallel determinations, the methods showed a good correlation. Each of them has its own advantage. Ågren and Lagerlöf's procedure is by far the most accurate of the three, but it consumes great quantities of alcohol and is more complicated to carry out than the other two. Both the simple methods proved reliable enough for clinical purposes. (The coefficient of variation was found to be the smallest

TABLE IV. LIPASE DETERMINATIONS

No.	Willstätter (units per 1 ml.) minutes									Leubner (per cent) minutes									Freudenberg (in 0.1 ml. of n/10 NaCH) minutes								
	0	10	20	30	40	50	60	70	80	0	10	20	30	40	50	60	70	80	0	10	20	30	40	50	60	70	80
1	16									11									35								
2	27–	20–	19–	27–	28–	24				35–	25–	21–	34–	37–	28												
2a	30									40																	
2b	26–	24								34–	30																
2c	20–	16–	26–	27–	23–	19–	17–	22		24–	12–	34–	36–	26–	18–	14–	26										
3	25–	20–	18–	17–	28–	27				32–	25–	20–	17–	37–	37				51–	46–	42–	40–	61–	61			
3a	34–	29								49–	39								70–	59							
3b	27–	32								36–	42								55–	64							
3c	24–	49								29–	68								50–	81							
4	38																		77								
5	16																		44								
6	21–	19–	26–	18–	21														47–	44–	55–	42–	46–				
6a	32–	43–								42–	64–																
6b	25–	17–	15–	22–	28–	29–				31–	15–	8–	27–	38–	38–												
6c	19–	29–	36–	27–						23–	38–	52–	35–														
6d	20–									25–																	
7	51–									71–																	
7a	36–									51–																	
7b	34–									45–																	
8	30–																		64–								
9	35–	40–	53–							50–	60–	72–															
9a	37–	39–	30–	29–	33–					55–	59–	38–	37–	47–													
9b	24–	19–	20–	19–	26–	26–				30–	22–	26–	20–	35–	37–												
10	13–									8–									30–								
11	21–									28–									48–								
11a	18–									20–									48–								
11b	27–									40–									60–								
11c	20–									22–									45–								
12	26–																		55–								
13	21–	15–	19–	17–	30–	39–	36–			25–	8–	20–	20–	40–	60–	50–			45–	35–	43–	34–	63–	69–	63–		
14	25–									33–									50–								
14a	16–									10–									40–								
14b	29–									36–									60–								
15	33–									40–																	
15a	38–									56–																	
15b	43–									65–																	
15c	32–									40–																	
16										68–									80–								
17	20–									24–									48–								
17a	34–									49–									70–								
18	19–																		45–								
18a	31–	24–	20–	17–	25–	32–	29–	35–	39–										64–	50–	48–	43–	55–	70–	59–	70–	77–
19	40–																		68–								
20	26–	29–	21–	33–	29–	28–													54–	62–	48–	65–	59–	55–			
21	20–									28–																	
21a	17–									16–									40–								
21b	28–									36–																	
22	24–									29–									60–								
23	34–	21–	17–	29–	38–					50–	25–	12–	38–	56–													
23a	40–	34–								61–	49–																
23b	38–	31–	26–	24–	22–	26–	28–			58–	40–	32–	29–	26–	35–	39–											
24	20–	26–	18–	17–	23–														47–	60–	43–	43–	51–				
25	27–	21–	18–																60–	49–	40–						
26	23–									30–									51–								
26a	16–									10–									37–								
26b	27–									34–									58–								
26c	29–									38–									61–								
27	49–									35–																	
28	38–									55–																	
28a	27–	33–	34–	27–						33–	45–	49–	35–														
29										70–									85–								
30										19–									40–								
31	26–									34–									55–								

TABLE IV—*Continued*

No.	Willstätter (units per 1 ml.) minutes								Leubner (per cent) minutes								Freudenberg (in 0.1 ml. of n/10 NaCH) minutes							
	0	10	20	30	40	50	60	70	80	0	10	20	30	40	50	60	70	80	0	10	20	30	40	50	60	70	80
32										67–									80–								
32a										36–									60–								
33	14–21–41–									9–25–56–									35–48–76–								
34	18–									21–									37–								
35	23–21–31–																		49–45–58–								
35a	35–21–15– 9–12–																		67–43–35–35–35–								
36	27–									34–									52–								
36a	40–									59–									73–								
37										8–									31–								
38										37–									66–								
39	42–									60–																	
39a	21–27–16–15–20–									26–34–14– 9–23–									45–54–38–34–40–								
39b	25–23–19–									32–28–22–																	
40										70–									75–								
41	28–									33–									57–								
42	36–																		70–								
43	17–									17–									35–								
43a	27–									38–									52–								
43b	31–									42																	
44	18–20–21–26–25–									21–25–25–34–34–									40–40–46–50–45								
45										63–									80–								
46	25–																		50–								
47	18–30–48–																		40–58–72–								
47a	29–																		68–								
	n = 182 mean = 26.4 ± 0.6 S.D. = 8.2 Coeff. of Var. = 31									n = 143 mean = 35 ± 1.3 S.D. = 15.3 Coeff. of Var. = 44									n = 113 mean = 53.2 ± 1.2 S.D. = 13 Coeff. of Var. = 24							

in Andersen's method. But, owing to the differences of the units, it would be misleading to judge the accuracy of the methods only by that coefficient.)

3. *Lipase:* 182 estimations were made with Willstätter's, 143 with Leubner's and 113 with Freudenberg's method.[16] (Many determinations were made also with the stalagmometric method, both in its original form and in the Willstätter modification. Its results, however, will not be presented because, in our hands, it yielded too wide variations even in the parallel determinations. It was felt that differences in the tributyrin solutions used might be responsible for this.) The results are shown in Table IV.

In Table IV, the values in the first column are given in Willstätter units, reckoned for a standard olive oil with a saponification number of 185.5/1 ml. of duodenal juice incubated for an hour. Figures in the second column reproduce percentile readings on the Zeiss stepphotometer and the results of Freudenberg's method indicate tenth units, i.e., the amount of 0.1 ml. of a tenth normal solution of sodium hydroxide required for titration of 5 ml. of cow's milk incubated with 1 ml. of enzyme solution for two hours. Neutral red was used as an indicator.

The mean was found to be 26.4 ± 0.6 with the Willstätter method, $35 \pm 1.3\%$ with Leubner's, and 5.3 ± 0.1 with the Freudenberg method. Other values are shown in Table II.

Willstätter's method was found the most satisfactory of the three, nearly always giving quite uniform results in the parallels. The Leubner method showed considerable

variations in the regions below 25% and above 50%. These, however, can be avoided by making a preliminary assay with the 1:50 enzyme solution originally described and adapting the dilution according to the result in such a way that the readings fall between 30 to 50%. This is the procedure to be adopted when dealing with duodenal juices of an abnormally low or high enzyme content. Freudenberg's method is the simplest and easiest to carry out of all the lipase determinations. Parallel estimations, if made with the same milk, showed little divergence. The use of different milks, however, considerably influenced the results. It is possible that the varying size of the fat droplets might be the cause of this. The use of a certain brand of homogenized milk may improve the accuracy of this method best suitable for routine examinations.

Summary of the characteristic values yielded by the different methods is given in Table II.

TABLE V

ENZYME VALUES IN DIFFERENT AGE GROUPS

Enzyme	Age Group Yrs.	Number of Observations	Mean
Amylase	below 2	46	1.03±0.07
	8–11	20	0.86±0.09
Trypsin	below 2	70	1.60±0.06
	8–11	30	1.85±0.13
Lipase	below 2	69	27 ±1.0
	8–11	24	25 ±1.6

CONCLUSIONS

1. The last line of Table II indicates the lowest values registered during the examinations. According not only to the above observations but to routine examinations of several hundred children and to the results of several authors working with the same methods, these isolated extreme figures by no means represent some low points of the average normal range but the lowest possible values to be encountered in healthy subjects. They can, accordingly, be regarded as threshold values and results below them must be considered pathologic. (With the possible exception of the Ågren-Lagerlöf trypsin determination. As the authors found values of 0.60 units in healthy persons, this figure should be substituted for the 0.08 found above.)

A knowledge of such lowest normal values yielded by the different methods of assay and expressing the results of pathologically low findings as fractions of these, makes it possible to measure and to compare the degree of any excretory dysfunction regardless of the kind of enzyme in question or the method of estimation used. It is, therefore, proposed to take the following values as 100%, and to express any value below these figures as their fraction, in per cents:

Amylase: 160 Wohlgemuth; 0.33 Ågren-Lagerlöf units

Trypsin: 128 Michaelis; 0.8 Ågren-Lagerlöf units; No. 4 tube (Fermi-Andersen)

Lipase: 13 Willstätter units, 8% (Leubner), and 3.0 Freudenberg units.

2. Several authors found that the activity of certain enzymes varies with age. In

order to examine this question, the means of the first 10 cases, representing the age group below two years and the 10 cases 38-47, subjects from 8 to 11 years of age, were calculated and tabulated in Table V.

As is shown by Table V, no differences of importance could be determined between

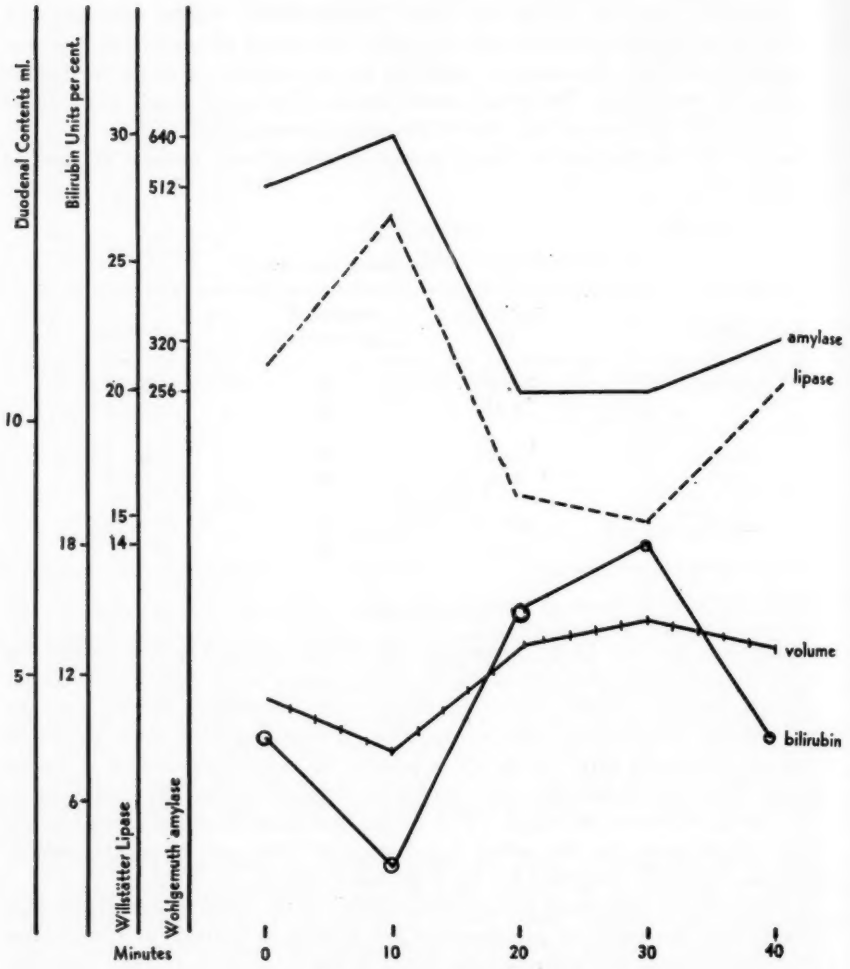

FIG. 1. Values of Case 39a.

the two age groups. There were certainly no variations in the lipase levels. The present results, being based on serial observations, can be considered more reliable than those in which only single examinations were performed. Naturally, no conclusions could be drawn regarding conditions in infancy as no subjects under 11 months of age were examined here.

3. A periodicity in the output of enzymes, as was described especially by Boldyreff,[17] could not be found. Analysing the 30 cases in which the duodenal juice was aspirated every 10 minutes for 30 to 80 minutes, fluctuations were certainly observed. These, however, showed no periodicity and it was felt that they were due to dilution of the pancreatic juice. Although a second tube was provided to prevent the gastric secretion from entering the duodenum, neither this measure nor the means to hinder the admixture of bile and enteric juice can be considered as wholly efficacious.

To prove this supposition, in five cases (6, 6b, 23b, 39a, and 44) not only the amount of each aspirated specimen and its fermentative activity were determined but

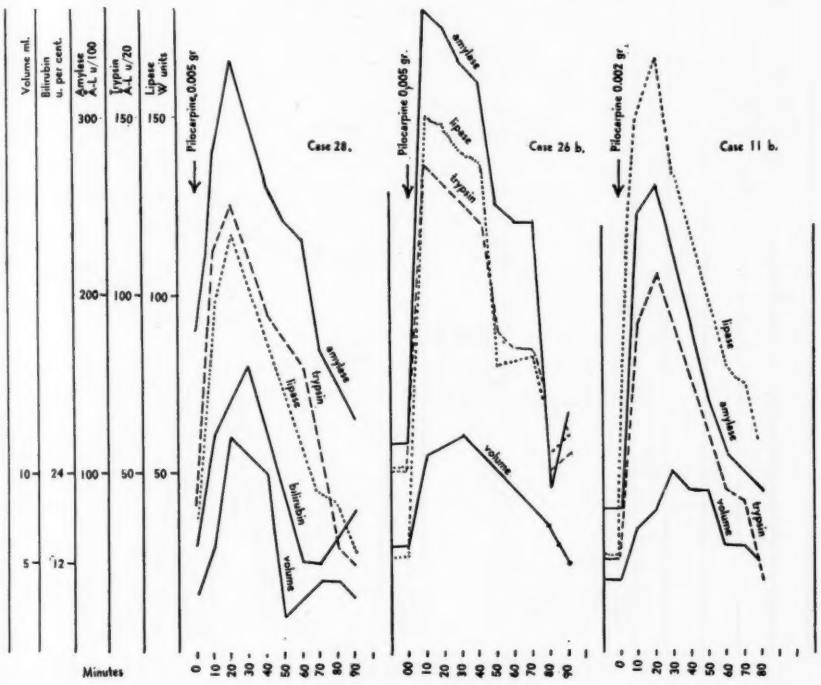

FIG. 2. Effect of Pilocarpine.

also the bilirubin content of each sample. Some values obtained in Case 39a, the most illuminating one of the five, are presented in Fig. 1.

It is obvious from Fig. 1 that there is a close connection between the amount of the juice and the bilirubin content, and it could be simply reckoned out that there was a constant output of a fluid with an average lipase activity of 31.5 Willstätter units per ml. in every 10 minutes, to which 0.5 to 3.0 ml. of another fluid containing about 6% units of bilirubin became admixed.

All the serial observations made prove that fasting secretion continuously occurs in healthy children and that the amount of enzymes put out is constant per units of time. This is in perfect accordance with Lagerlöf's[18] findings.

4. Many authors observing animals and also human subjects found that there is

a parallelism in the output of the three enzymes. The five cases discussed above make it probable that all variations in the fermentative activity of a fasting duodenal juice are chiefly due to variations in the concentration of the enzymes caused by dilution with bile, or succus entericus and gastric juice which has escaped the gastric tube. It was, however, striking that, through periods of an hour and more, the curves of the three enzymes ran parallel in all the present cases and in all healthy children observed. There was practically no exception from this rule.

It seemed interesting to investigate whether this is true following stimulation and inhibition of pancreatic excretion. For stimulation, pilocarpine hydrochloride was used.

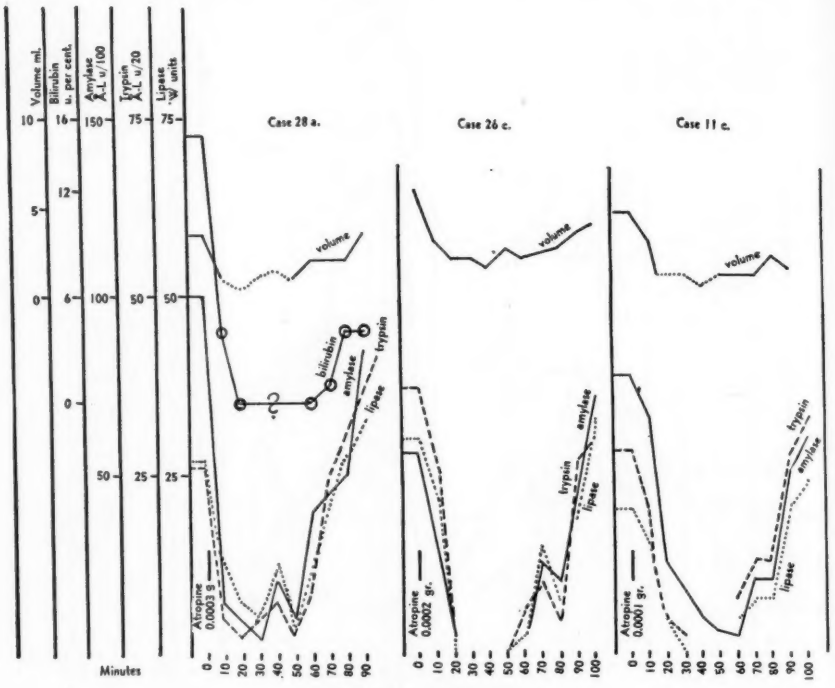

FIG. 3. Effect of Atropine.

The drug was administrated to three subjects (11b, 26b and 28). The results are shown in Fig. 2.

The same subjects were again observed after some days (11, 16 and 7, respectively), and this time atropine sulphate was given. Fig. 3 shows the values registered.

It is quite as clear from Fig. 2 and Fig. 3 as from Baxter's[19] rabbit experiments that the excretion of all the three enzymes is equally affected by variations of the secretory process, whether these were provoked by stimulation or inhibition. In addition to this, every case in which serial observations were made evidently proves that whatever variation of activity occurred happened simultaneously with each enzyme. This phenomenon occurred so regularly in all the present subjects and in every healthy child observed that cases, in which fluctuations of a single enzyme do not correspond within the given limits

of a short experimental period with the variations of the other two, must be considered pathologic. As it will be seen in future reports on enzyme secretion in disease, this strict parallelism exists almost exclusively in healthy subjects. Conditions become entirely different as soon as the external secretion of the pancreas is affected by some pathologic process.

5. It is still common belief that the production of enzymes is adapted to the food given, i.e., that the preponderance of any constituent of the diet increases the production of the enzyme splitting the material in question while the output of the other two is lessened. The theory, first advocated by Pavlov[20] but soon rejected by his own school,

TABLE VI

EFFECT OF UNBALANCED DIETS

Case No.	Diet	Days of Experiment	Amylase Wohlgemuth units	Trypsin Ågren-Lagerlöf units/20	Lipase Willstätter units
9a	Carbohydrate		1323	51	43
9a		3	563	30	24
9b		16	448	28	22
21	Carbohydrate		448	32	20
21a		2	192	58	17
21b		20	384	49	28
35	Protein		201	20	25
35a		7	358	20	18
36	Protein		1024	68	27
36a		14	512	37	40
15	Fat		448	29	33
15a		3	640	36	38
15b		7	1024	38	43
15c		13	640	55	32
43	Fat		192	18	17
43a		7	256	23	27
43b		17	512	41	31

is still held by many authors (e.g., Freudenberg[21]). To examine this problem, six children (9, 21, 35, 36 and 43) were, after a preliminary examination, given unbalanced diets. The results are shown in Table VI.

As can be seen from Table VI, some changes could certainly be recorded but these can under no condition be ascribed to the effect of the diets. To quote examples, in the first case (9) there was a parallel decrease in all the three enzymes while a diet consisting mainly of carbohydrates was fed. All values recorded on the first day were, however, exceptionally high, and there was only little change after the third day. In any case, no increase in the amylase, or decrease in the other two enzymes, occurred. In a case in which fat prepondered in the diet (15) on the seventh day it seemed

that all values steadily increased. On the 13th day, however, amylase and lipase fell back to their levels registered on the third day. Trypsin, on the other hand, showed, instead of decreasing, a further increase, but this increase remained well within normal limits. All in all, the changes found during the administration of different diets were irregular and not substantial and could by no means be connected with the type of food eaten. Indeed, it was found permissible to include the results of these observations among those of the normals. It has, however, to be noted that the duration of the observations was somewhat shorter than that of some investigators recording contradictory results.[22]

Finally, it should be emphasized again that all the above data were found in healthy and normal children and that these conditions are thoroughly different in most pathologic conditions.

Summary

Serial analyses of duodenal juices of 47 children were made by parallel estimations with different methods of amylase, trypsin and lipase assay for studying normal conditions and to establish a common denominator which would, independently from the method of estimation used and from the enzyme in question, indicate the normal or pathologic character of the findings. On the basis of more than 1,200 determinations it is proposed to take the lowest values recorded as 100% and to express any value below these figures as their fractions in per cent.

No differences of importance could be found between the enzyme values of different age groups and there were certainly no variations in the lipase levels.

No periodicity could be observed in the output of enzymes. Fluctuations occurred but these showed no periodicity and it could be proved that they were due to dilution of the pancreatic juice by bile. Fasting secretion continuously occurred in these healthy children and the amount of enzymes put out was constant in units of time.

A strict parallelism in the output of the three enzymes was observed in all the present cases. This holds true also following stimulation by pilocarpine and inhibition by atropine and whatever variation occurred happened simultaneously with each enzyme.

Six children were given unbalanced diets to determine whether the production of enzymes is adapted to the food given. The changes found during and after the diets could by no means be connected with the type of food eaten.

It is emphasized that all the above data were found in healthy and normal children and that the conditions described are thoroughly different in most pathologic conditions.

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SPANISH ABSTRACT

Enzimas Pancreáticos: Producción Normal y Comparación de Diferentes Métodos de Valoración

Análisis de serie de jugos duodenales de 47 niños fueron hechos mediante cálculos paralelos con diferentes métodos de valoración de amilasa, tripsina y lipasa para estudiar las condiciones normales y establecer un común denominador, el cual, independientemente del método de cálculo usado y del enzima de que se trata, indicase el carácter patológico o normal de los descubrimientos. A base de más de 1,200 determinaciones se propone tomar los valores más bajos registrados como 100% y expresar culaquier valor menor que esos números como sus fracciones en por ciento.

No se pudo encontrar diferencia de importancia entre los valores de enzima de grupos de diferente edad y no hubieron variaciones en las cantidades de la lipasa.

No se pudo observar periodicidad en la producción de los enzimas. Hubieron fluctuaciones, pero éstas no mostraron periodicidad y se pudo probar que eran debido a la dilución del jugo pancreático por la bilis. Secreción de ayuno ocurrió continuamente en aquellos niños sanos y la cantidad de enzimas producidos fué constante en unidades de tiempo.

Se observó un paralelismo estricto en la producción de los tres enzimas en todos los casos presentes. Esto mismo sucedió también después de la estimulación por la pilocarpina e inhibición por atropina y toda variación que se presentó sucedió simultaneamente con cada enzima.

Se les dió dietas irregulares a seis niños para ver si la producción de enzimas se adapta al alimento dado. Los cambios que se encontraron durante y después de las dietas no se pudieron conectar con el tipo de alimento consumido.

Hay que indicar que toda la información arriba citada fué encontrada en niños normales y sanos y que las condiciones descritas son completamente diferentes en la mayor parte de las condiciones patológicas.

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AUREOMYCIN IN STAPHYLOCOCCIC MENINGITIS COMPLICATING SUBARACHNOID HEMORRHAGE IN SICKLE CELL ANEMIA

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THIS presentation has a dual purpose. The first is to report the rare occurrence of subarachnoid hemorrhage as a complication of sickle cell anemia. Only eight such cases have been reported, five of which were in children. The second purpose is to record the use of aureomycin* in the successful treatment of the staphylococcus albus meningitis which developed in this patient. As far as can be determined, this is the first reported case of meningitis to be treated with aureomycin.

The neurologic complications of sickle cell anemia in children were not recognized until 1923 when Sydenstricker, Mulherin and Houseal[1] reported hemiplegia in a five year old Negro child with sickle cell anemia. In 1940, Hughes, Diggs and Gillespie[2] in reviewing the literature found 25 cases of involvement of the nervous system in sickle cell anemia, and added six cases of their own. The type and frequency of the manifestations in the 31 cases were:

Drowsiness, stupor or coma	16
Hemiplegia	14
Aphasia	9
Headache	8
Convulsion	8
Stiffness of neck	8
Pain in nuchal region	7

Cook[3] observed in 1930 the first instance of subarachnoid hemorrhage in a child with sickle cell disease. Pertinent information concerning the eight cases reported to date are listed in Table I.

CASE PRESENTATION

D. J., an 11 yr. old Negro boy, entered the pediatric ward of the hospital, his 9th admission because of a sickle cell crisis. His presenting symptoms were headache, coryza and dyspnea which were of 24 hrs.' duration.

Physical examination revealed an acutely ill, dyspneic, but fairly well developed and nourished boy of the approximate stated age. Temperature 39.2°C., pulse 104/min., respiration 24/min. There was congestion of the nasal mucosa. Heart was enlarged both to the right and to the left, and there was a harsh, systolic murmur heard over the entire precordium, loudest at the mitral area. Blood pressure was 110/50 mm.Hg. Liver edge was 5 cm. below the costal margin and was slightly tender. Spleen was not palpable. Sclerae were icteric.

Hemoglobin was 6 gm./100 cc. blood, RBC count was 1.9 million and the sickling test was positive. The patient received two blood transfusions of 300 cc. each, following which his RBC count rose to 2.95 million and Hgb. to 9.2 gm. Temperature fell to normal, liver edge receded, and previous symptoms disappeared. Electrocardiogram revealed a P-R interval of 0.19 sec. with a rate of 84. Roentgenologic studies of the heart indicated right and left ventricular enlargement, prominence of the pulmonary conus, and left auricular enlargement. These cardiac findings were essentially the same as had been present during the 5 year period he was under observation. The P-R interval

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* The aureomycin was supplied by Lederle Laboratories Division, American Cyanamid Company.

TABLE I

SUMMARY DATA CONCERNING PATIENTS WITH SICKLE CELL ANEMIA DEVELOPING SUBARACHNOID HEMORRHAGE

Authors	Age in Years	Sex	Presenting Symptom or Sign	Character of Spinal Fluid	Outcome	Comment
Graham[4]	30	M	Headache, nuchal rigidity	Bloody, later xanthochromic	Died	No gross brain abnormality was found at autopsy but cerebrospinal fluid was xanthochromic.
Cook[3]	7	M	Sudden loss of consciousness	Xanthochromic	Died	Subarachnoid hemorrhage with cerebral softening found at autopsy.
Arena[5]	6	M	Severe headache, coma	Bloody	Recovered	Residual spastic hemiplegia.
Kampmeier[6]	13	M	Convulsions, then coma	Bloody, later xanthochromic	Recovered	Residual spastic hemiplegia; patient had 3 previous episodes of stupor and coma.
Bridges[7]	7	F	Headache, coma	Bloody, slightly xanthochromic	Died	Subdural and subarachnoid hemorrhages with large areas of encephalomalacia found at autopsy. Three years previously patient had right hemiplegia.
Walker and Murphy[8]	12	M	Severe headache, then coma	Not determined	Died	Massive hemorrhage into right lenticular nucleus with rupture into ventricular system demonstrated at autopsy.
Wertham,* Mitchell and Angrist[9]	31	M	Severe headache, nuchal rigidity, coma	Xanthochromic	Died	Rupture of congenital aneurysm of left middle cerebral artery found at autopsy.
Thompson, Wagnet, and MacLeod[10]	20	M	Headache, convulsion, coma	Bloody	Died	Subarachnoid hemorrhage, cortical hemorrhages, areas of encephalomalacia found at autopsy.

* This may not represent a true complication in view of the autopsy findings.

at times returned to within normal limits. ESR (Wintrobe) on admission was 39 mm. in 60 min. (corrected) and 12 days later it was 4 mm. Hgb. became stabilized at about 8.5 gm./100 cc. blood. After transfusion the serum bilirubin was 2.1 mg./100 cc. and the icterus index was 26.

At 9 p.m., one month after admission, while the intern was talking to him the patient suddenly cried out and complained of severe frontal headache. Two hours later he had a convulsion following which he was comatose. He received continuous oxygen therapy and 250 cc. of whole blood with no change in his condition. The next morning his temperature was 38.1°C. and there was stiffness of the neck and back. No localizing neurologic signs developed and coma persisted. Grossly bloody fluid was obtained on spinal drainage and the diagnosis of subarachnoid hemorrhage as a complication of sickle cell anemia was confirmed. Blood count at that time revealed a Hgb. 8.3 gm., RBC count 2.95 million, and WBC count 25.1 thousand with neutrophiles 84%.

Two days later the temperature rose to 40.6°C. The patient was found to have a profuse purulent nasal discharge which on culture revealed Staph. aureus hemolyticus, coagulase positive. He continued to have fever up to 40.5°C. and developed opisthotonus. It was decided that the height of his temperature and the stiffness of his neck were out of proportion to that expected in subarachnoid hemorrhage, so another lumbar tap was performed 5 days after the initial examination. The spinal fluid was still grossly bloody and on direct smear numerous staphylococci were seen and on culture Staph. albus nonhemolyticus, coagulase negative was elicited. The cerebrospinal fluid glucose was 33.8 mg./100 cc. Penicillin 50,000 units in 10 cc. normal saline was given intrathecally each day and 100,000 units intramuscularly every 3 hours. In addition, he received sulfadiazine 1.5 gm. every 4 hours.

The organism isolated from the spinal fluid was found to be sensitive to 0.5 u. of penicillin, 10 mg. of sulfadiazine, and 2 u. of streptomycin per cc. As the bacteria were fairly sensitive to streptomycin

the patient was placed on 0.3 gm. of this drug every 3 hours intramuscularly, and 100 mg./day intrathecally. The patient received the combined therapy of all 3 drugs for 12 more days, during which time he remained in profound coma and continued to have temperature elevations between 38.9° and 40.0°C. and severe opisthotonus persisted. He received intravenously his daily requirements of fluid, protein, carbohydrate, calories and water soluble vitamins. He had no adverse reaction to the intrathecal therapy. His spinal fluid was examined daily and each time numerous organisms were found on direct smear and culture. The grossly bloody appearance of the spinal fluid cleared gradually, becoming xanthochromic within 8 days.

Ten days after the start of this therapeutic regime, the cerebrospinal fluid had 4,325 white blood cells per cmm. with 96% neutrophiles. A smear of the fluid revealed numerous organisms; on culture Staph. albus was found—this being reported by two different laboratories. Three days later the cerebrospinal fluid glucose was 64.3 mg./100 cc. Direct smear of the spinal fluid for the 11th time revealed numerous organisms which on culture proved to be Staph. albus. The next morning the patient's condition was unchanged and inasmuch as he had failed to respond to sulfadiazine, streptomycin and penicillin, it was decided to discontinue the therapy employed.

Since at this point it seemed to the members of the staff that the patient's prognosis was hopeless, it was thought justifiable to exhibit an experimental antibiotic agent. Detailed study in the laboratory disclosed Staph. albus isolated was sensitive to 0.3 μgm. of aureomycin per cc. Consequently, the patient was started on aureomycin 20 mg. intramuscularly every 8 hours. Within 2 days, the patient improved remarkably and already was taking all fluids by mouth. After 5 days the spinal fluid revealed only 5 cells per cmm., no organisms were seen on smear, and cultures were negative. The spinal fluid glucose was 85.6 mg. and the protein was 140 mg./100 cc. The patient was afebrile and able to say a few words.

Aureomycin was given for a total of 10 days, by the end of which time the patient had become alert and could recognize people. One week after aureomycin was stopped, the spinal fluid revealed: no cells, no organisms on smear, no growth on culture, 77 mg. glucose, and 22 mg. protein/100 cc. Twelve days later, the patient was up and about playing with other children on the ward. A neurologic examination revealed findings within normal limits. Hemoglobin had stabilized at 7.3 gm., and his serum bilirubin was 3.2 mg./100 cc. indirect. The electrocardiographic and fluoroscopic findings of the heart were unchanged. Psychologic examination revealed a high grade mental deficiency but of a pattern that was in marked contrast to that of primary deficiency. The pattern was compatible with selective impairment of psychologic function. A repeat test was done 3 months later and showed that the mental age had advanced 1 year, but the pattern was similar to the previous test.

Discussion

Subarachnoid hemorrhage in sickle cell disease.—In this disease the fundamental lesions in the brain are similar to those occurring in the spleen and other organs. The arteries become narrowed due to thickening of their walls. The narrowed vessels become thrombosed and infarction may result in such extensive fibrosis that the spleen may weigh only seven or eight grams. Hughes, Diggs and Gillespie[2] state the most common and constant cerebral finding at autopsy is congestion with sickled erythrocytes and dilatation of the peripheral cerebral blood vessels. Multiple thromboses of small blood vessels in the cortical grey matter and in the meningeal vessels occur and sometimes there develops thrombosis of the large dural sinuses and cortical branches of the cerebral arteries, particularly the middle cerebral arteries. In the larger arteries and arterioles which supply blood to the cerebral cortex they found alterations in the walls which include intimal proliferation, fragmentation and reduplication of the intima, fibrosis and hyalinization of the media. Occasionally, hemorrhage into the media occurred. Both fresh and organized thrombi often were found in the narrowed vessels. In the cortical and convolutional grey matter and to a lesser extent in the white matter adjacent to it, there was connective tissue proliferation and areas of gross atrophy with a practical absence of pyramidal cells.

The cerebral symptoms produced by the thrombosis of a vessel as a result of sickle

cell anemia do not differ from symptoms produced by thrombosis from other causes. In fact, in cerebrovascular accidents in children and young adults of the Negro race, sickle cell anemia must be seriously considered as the underlying cause. More and more instances of hemiplegia, coma, convulsions, and subarachnoid hemorrhage are being recognized as a complication of sickle cell anemia. The prognosis of a patient with subarachnoid hemorrhage complicating sickle cell anemia is poor. Only three of the nine patients reported have survived and two of these had residual hemiplegia. The patient in this study has impairment of his mental capacities.

Aureomycin in relation to staphylococcal meningitis.—The occurrence of staphylococcus albus meningitis in itself is rather unusual, but the masking of these symptoms at the onset by the subarachnoid hemorrhage appears remarkable indeed. The diagnosis of meningitis was delayed a day or two because the rigid neck and the elevation of temperature were considered to be due to the cerebral accident. The process was believed to be metastatic from the purulent nasal infection although roentgenograms of the paranasal sinuses revealed no abnormality.

The patient failed to respond to the combined administration of penicillin, streptomycin and sulfadiazine including intrathecal therapy for 12 days. Although no work had been published with regard to aureomycin in meningitis, members of the research staff of Lederle Laboratories had found that this antibiotic was effective against staphylococci. Since the spinal fluid of this patient showed staphylococci on 11 consecutive direct smears and cultures, it was decided to discontinue all previous therapy and use aureomycin exclusively. The patient was placed on an arbitrary intramuscular dose of 2 mg./kg./24 hours in three divided doses. The oral form of the drug was not available. There were no untoward reactions to the intramuscular administration of this drug.

Blood level determinations of aureomycin by a technic similar to that used for penicillin were attempted, but were unsuccessful. It was noted by the bacteriologist that *in vitro* aureomycin was inactivated by human serum. Subsequently, Bryer and coworkers[11] have reported *in vitro* experiments in which it was found that in the presence of a 50% concentration of serum 50 times more aureomycin was required to inhibit growth of bacteria than when broth alone was used.

Lankford and Lacy[12] found in 21 strains of staphylococci isolated from 19 patients in this hospital that the sensitivity of the organisms to penicillin, streptomycin or aureomycin was as follows:

Antibiotic	Range of Sensitivity
aureomycin	0.08 to 0.3 μgm./cc.
streptomycin	0.3 to 3.0 μgm./cc.
penicillin	0.006 to 1.0 μgm./cc.

Staphylococci isolated from the spinal fluid of this patient were found to be the most resistant to aureomycin of all the strains tested.

The feature which probably played a role in the excellent response of the patient to aureomycin was the decision to discontinue all other therapeutic agents. In the laboratory[12] it was found that when penicillin and aureomycin or streptomycin and aureomycin were combined *in vitro* the result was a decrease in the effectiveness of each drug on the staphylococci. The clinical implications of this are apparent because of the increasing trend to use combinations of antibiotics. On the basis of these results it seems logical to emphasize that more effective results in the treatment of staphylococcal infections may be obtained if aureomycin is used as the sole antibiotic agent.

SUMMARY

The rare occurrence of a spontaneous subarachnoid hemorrhage in an 11 year old Negro boy with sickle cell anemia is recorded. Of the eight reported cases five have occurred in children. In the study of sickle cell anemia it is evident there is an increasing awareness of this as well as other neurologic complications.

This patient developed staphylococcus albus meningitis which for 12 days resisted combined penicillin, streptomycin and sulfadiazine therapy. The response to aureomycin as a sole therapeutic agent was dramatic, and this represents the first reported case of meningitis treated with this drug.

The use of aureomycin as the only antibiotic in this staphylococcic infection seems to have been fortunate in view of the laboratory findings. *In vitro* studies disclosed that when penicillin and aureomycin or streptomycin and aureomycin were combined, the result was a decrease in the effectiveness of either drug on staphylococci.

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SPANISH ABSTRACT

Aureomicina en Meningitis Estafilocócica Complicando Hemorragia Subaracnoide en Anemia Hematíe Falciforme

Se relata un caso raro de una hemorragia subaracnoide en un muchacho negro de 11 años de edad con anemia hematíe falciforme. De los ocho casos reportados, cinco han ocurrido en niños. Es evidente que en el estudio de la anemia hematíe falciforme se da uno más y más cuenta de esto lo mismo que de otras complicaciones neurológicas.

Este paciente desarrolló meningitis albus estafilocócica la que por 12 días resistió la terapia combinada de penicilina, estreptomicina y sulfadiazina. La respuesta a la aureomicina como único agente terapéutico fué dramatica, y éste representa el primer caso de meningitis que se ha tratado con esta droga.

El uso de la aureomicina como único antibiótico en esta infección estafilocócica parece haber tenido éxito en vista de los descubrimientos de laboratorio. Los estudios "in vitro" demostraron que cuando la penicilina y la aureomicina o la estreptomicina y aureomicina fueron combinadas, la efectividad de cualquiera de las drogas sobre los estafilococos disminuyó.

Children's Hospital

RUPTURE OF ANEURYSM OF THE CIRCLE OF WILLIS IN THE NEWBORN

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ACUTE spontaneous cerebral vascular accidents in infants are extremely rare. Despite voluminous literature on cerebral aneurysm, no case in the newborn period has been found.

The earliest recorded instance[1] was a patient with congenital polycystic disease of the kidneys who died at 13 weeks of age. The aneurysm was an evagination from the ventral wall of the basilar artery, one mm. in diameter, at the level of the bifurcation into the two posterior cerebral arteries.

A history of mild trauma may precede the rupture of an aneurysm. A 23 day old male infant was admitted to Childrens' Memorial Hospital after an accidental blow on the head from the elbow of his mother. He became cyanotic rapidly, developed rapid breathing and died four hours after admission. Postmortem subdural tap and lumbar puncture yielded bloody fluid. Autopsy revealed a ruptured aneurysm arising from the circle of Willis. The exact location was not determined. The aneurysmal sac was divided into four fairly well demarcated layers. There was no smooth muscle in the wall. Other instances of mild trauma producing rupture were the 4½ year old boy, reported by Herman,[2] who "headed" a light rubber toy ball, and the 6 year old boy with pneumococcal meningitis, reported by Sullivan,[3] who died from a ruptured basilar artery. Talbot,[4] in 1919, reported the fatal rupture in a 9½ year old boy of an aneurysm of the beginning of the left cerebral artery. (This patient had violent spasms of coughing from pertussis.)

Severe exercise or injury was apparently responsible for two other ruptures. A 12 year old boy reported by Schreiber,[5] collapsed after rounding the bases in a ball game and died five days later of a fatal subarachnoidal hemorrhage. Dial and Maurer[6] record the rupture of an aneurysm of the right vertebral artery in a 2 year old who had apparently recovered from a skull fracture. After discharge from the hospital on the 7th day, he became irritable and developed convulsions, dyspnoea and cyanosis. Death occurred 36 days after the accident.

Many excellent articles have appeared in the literature since Fearnsides'[7] classical paper in 1916. McDonald and Karb[8] have reviewed the literature and charted the location of 1,125 verified cases of ruptured intracranial aneurysms.

Martland[9] charted his cases and reported that 2% of all sudden and unexplained deaths encountered by medical examiners were due to spontaneous subarachnoid hemorrhage; that 70% of these were due to ruptured "berry" aneursyms, and that associated congenital defects such as polycystic disease of the kidneys and liver support the theory of congenital origin. Bremer,[10] from a thorough embryologic study, showed that "berry" aneursysms may be remnants of fetal cerebral plexuses; that proximal members of such plexuses may enlarge, while their distal continuations degenerate and thus become aneu-

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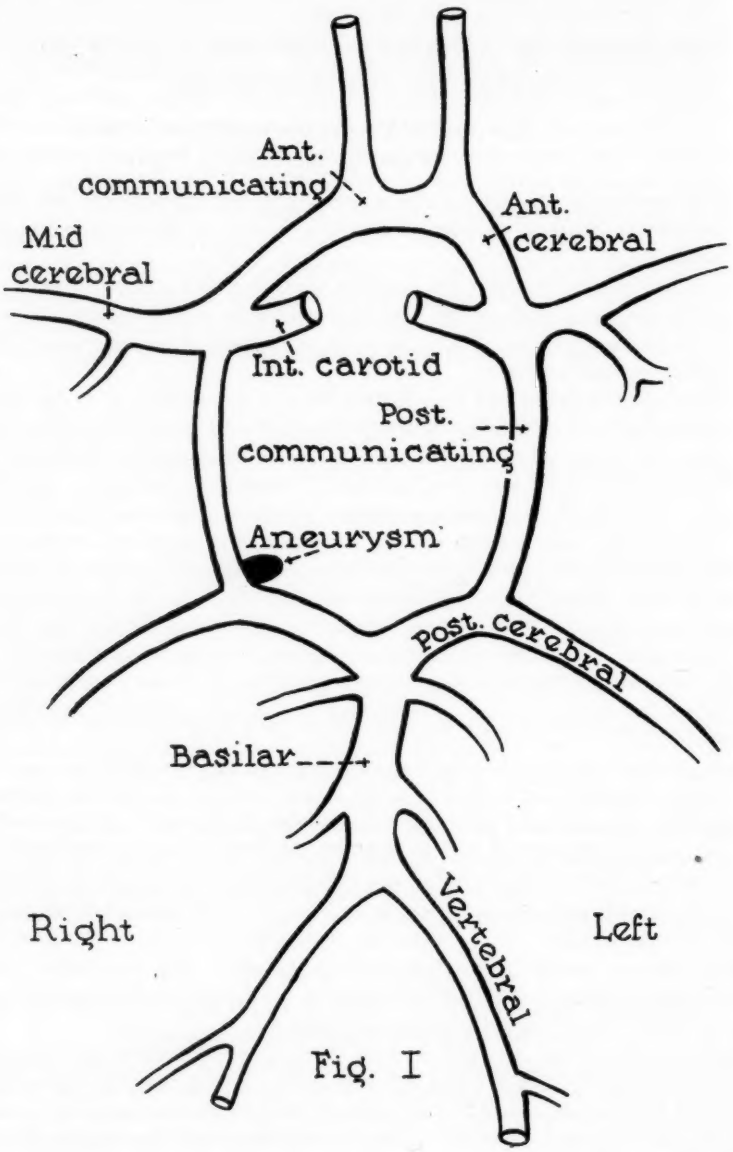

FIG. 1. Diagrammatic sketch of circle of Willis showing approximate location of ruptured aneurysm.

rysmal pouches. Other aneurysms may develop at the fork of the vessels. If these forks lack the media, the rapid spreading and widening may produce local aneurysms. Both types may be true congenital aneurysms.

Hodes, Perryman and Chamberlain,[11] in a report on cerebral angiography, accept Bremer's thesis that most "berry" aneurysms (80%) are congenital. These arise at the site of primitive embryologic vessels which have completely absorbed, leaving "nubbins" on the arterial trunk which later enlarge and become aneursysmal.

Richardson and Hyland,[12] referring to Forbus' work[13] in 1930, believe that the medial defects are probably developmental. They have described the syndrome well.

Forbus demonstrated congenital defects in the cerebral, coronary, mesenteric and pulmonary arteries. He recently stated[14] that an aneurysm does not date from embryonic life, but develops after birth and is therefore acquired.

The characteristic syndrome as described in the adult consists of sudden headache, followed quickly by an apopleptic seizure and sudden loss of consciousness and deep coma. The spinal fluid is invariably bloody. Localized findings, such as pressure symptoms produced by aneurysm affecting the intracranial nerves, are well described by Hodes, Perryman and Chamberlain.[11]

Case Report

These observations are on twins, born in Evanston Hospital, who died in the first few days of life. The smaller and younger, a female weighing 2400 gm., died 31 hrs. after birth. Unfortunately, a complete autopsy was not done. Atelectasis of both lungs was found, but the brain was not examined.

The male, weighing 2850 gm., died 64 hrs. after birth. The infants presented identical symptoms, except that those of the smaller female were found more severe at birth and were more rapidly progressive.

Delivery was normal. Duration of labor in the first stage was 5 hrs., 15 min. Premedication was demerol, 100 mg., and scopolamine, 0.4 mg. Nitrous oxide was administered for 30 min. Delivery was by low forceps.

Both infants were cyanotic at birth and were revived with difficulty. Cyanosis was partially relieved by oxygen. The female was immediately placed in an incubator with a high content of oxygen. The male was given oxygen by mask.

At the time of the first examination, an expiratory grunt was present in both infants together with suprasternal and diaphragmatic retraction. Breath sounds were clear anteriorly in the male, but suppressed or faint in the female and heard distinctly only in the left axillary region. In addition, the male at times had manifested a high pitched cry. There was no bulging of the fontanelles or rigidity of the neck.

The fatal course was more rapid in the female who became intensely cyanotic when out of oxygen. The boy appeared to improve for 48 hrs. and then became progressively weaker, pale and dyspneic until death.

Complete autopsy on the male revealed:

Brain—There was intense meningeal congestion over both cerebral hemispheres and a small amount of subarachnoid hemorrhage bilaterally. About the base of the brain and brain stem, there was a large accumulation of subarachnoid blood which reached a thickness of 0.5 cm. in some areas and which extended into the cervical canal. No hematoma could be palpated in the brain substance. A definite aneurysmal dilatation, thin-walled and about 2 mm. in diameter, was found at the junction of the posterior cerebral artery and posterior communicating branch on the right (Figure 1). This was the obvious source

of the hemorrhage which was the greatest in the contiguous portions of the arachnoid space. No other definite lesion was found.

Lungs—Lungs revealed primary atelectasis and bilateral bronchopneumonia.

Summary

A case of spontaneous cerebral hemorrhage from an aneurysm of the circle of Willis is reported in the male of newborn twins. The smaller female twin died earlier with similar symptoms and signs, but no intracranial autopsy was performed.

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Spanish Abstract

Ruptura de Aneurisma del Círculo de Willis en el Recien-nacido

Se presenta un caso de ruptura de aneurisma del círculo de Willis que ocurrió en el recien-nacido. Tales accidentes vasculares espontaneos son extremadamente raros; no se ha encontrado relato de un tal fenómeno.

Este caso ocurrió en el varon de un par de gemelos, ambos de los cuales murieron dentro de 31 hora después del nacimiento, cada uno de los gemelos presentó síntomas idénticos. Desgraciadamente no se hizo la autopsia de la cabeza de la hembrita gemela. La que se le hizo al varoncito gemelo reveló un aneurisma roto en el punto de unión de la arteria cerebral posterior y el ramo comunicante posterior a la derecha.

Este caso ayuda a coroborar la opinion de que la mayor parte de los aneurismas craneales "berry" son de origen congénito.

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OVARIAN TUMORS IN CHILDHOOD

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SEVERAL well known studies attest to the infrequency of ovarian tumors during the childhood age period. Lanman[1] in 1929 reported that only five cases had been observed among 12,260 children under 12 years of age admitted to the surgical service of the Children's Hospital of Boston within 10 years. A review of the literature by Witzberger and Agerty[2] in 1937 revealed that at that time only 186 cases had been reported in children up to 10 years of age. Kelly[3] in 1940 reported that among 434 cases of malignant ovarian tumors observed at Memorial Hospital in New York, none had occurred before 10 years of age, and between the 10th and 15th year only four cases were found.

This discussion is concerned with 14 previously unreported cases which have been observed on the pediatric and surgical services of St. Luke's, St. Vincent's and Memorial Hospitals in New York City. The first two institutions are large general hospitals with active pediatric and surgical services. Memorial Hospital treats only patients with neoplastic diseases. Two cases are from St. Vincent's, eight from St. Luke's and four from Memorial Hospital. The clinical data of these 14 cases are summarized in Chart I.

CLINICAL DATA

Age: The youngest patient was 1 yr. of age; the oldest 14. Four patients were under 10 yrs. of age.

Anatomic diagnoses: Ten of these were cysts classified as: dermoid, 5; follicular, 2; fimbrial, 1; parovarian, 1; pseudomucinous, 1. The other 4 tumors were: malignant teratoma, embryonal adenocarcinoma, choriocarcinoma, mesonephric adenosarcoma.

Symptomatology: Only 1 patient had no symptoms. She was a child of 4 yrs. who in the course of an abdominal examination during an attack of gastroenteritis was found to have a moveable tumor. The relationship of the tumor to the intestinal symptoms may be only surmised. She recovered from her brief illness. Her physician advised re-examination after recovery, but this was not done. She had no complaints for 1 yr. when another intestinal upset occurred. The tumor was again identified and operation permitted. A dermoid cyst with a long pedicle was found.

Only 1 child had bladder symptoms.

Six had abdominal pain of varying intensities, and in 5 enlargement of the abdomen was the reason the patients sought medical care.

One girl of 14 had irregular menses, another of 13 had not menstruated.

Only 1 complained of loss in weight.

Clinical Diagnoses: A presumptive diagnosis of ovarian tumor was made preoperatively in 10 cases by the finding of a mass by abdominal or rectal examination or both. No mass was found preoperatively in 4 cases.

The laboratory findings of significance were in 2 cases of dermoid cysts in which roentgenograms showed calcified shadows in the masses suggesting cartilage or bone.

Treatment: The interval from onset of symptoms to treatment varied from 6 days to 1 yr. Only 5 children were treated 1 mo. or less from the apparent beginning of clinical evidence of disease. The treatment consisted of complete oophorectomies on the affected side with 1 excep-

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From the Children's Tumor Registry, Memorial Hospital, New York, N.Y.

Read before the Sections on Pediatrics and Obstetrics and Gynecology of the American Medical Association, Chicago, Ill., June 25, 1948.

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CHART I

OVARIAN TUMORS IN CHILDHOOD

No.	Age yrs.	Diagnosis	Symptomatology	Menses	Physical S.	Onset/R_x	Treatment	Result	Survival/Onset
1	1	Mesonephric adenosarcoma	Enlarged abdomen	—	Mass LLQ	2 wk.	Oophorectomy	Abd. Rec. Died	4 mo.
2	4	Dermoid cyst	None	—	Moveable abdominal mass (4 cm.)	1 yr.	Oophorectomy	Living	10 mo.
3	6	Dermoid cyst	Abdominal pain	—	Abdominal pelvic mass	3 mo.	Oophorectomy	P. op. unevent.	—
4	9	Follicular cyst	RLQ pain	—	None	3 wk.	Partial oophorectomy	P. op. unevent.	—
5	10	Dermoid cyst	Abdominal pain	—	Tender RLQ	10 wk.	Oophorectomy	P. op. unevent.	—
6	10	Dermoid cyst	Enlarged abdomen	—	Moveable mass RLQ (6 cm.)	6 mo.	Oophorectomy	Living	11 yr.
7	10	Embryonic choriocarcinoma	Urinary frequency	—	Abdominal mass (5 cm.)	2 wk.	Oophorectomy	Abd. Rec. Died	5 mo.
8	10	Embryonal adenocarcinoma	LLQ pain	—	Abdominal mass (20 cm.)	3 mo.	Oophorectomy X-ray Oreton	Died	7 mo.
9	10	Malignant teratoma	Weight loss	—	Abdominal mass (1625 gm.)	3 mo.	Oophorectomy	Living	9 yr.
10	13	Fimbrial cyst	RLQ pain	N	Tenderness No mass	6 d.	Oophorectomy	Living	11 yr.
11	13	Parovarian cyst	Enlarged abdomen	O	Abdominal mass	6 wk.	Oophorectomy	P. op. unevent.	—
12	13	Dermoid cyst	Enlarged abdomen	N	Abdominal mass	2 mo.	Oophorectomy	Living	7 yr.
13	14	Pseudo-mucinous cyst	Enlarged abdomen	N	Abdominal rectal mass	1 yr.	Oophorectomy	P. op. unevent.	—
14	14	Follicular cyst	RLQ pain	1	Tenderness No mass	1 mo.	Oophorectomy	P. op. unevent.	—

tion. This child had a follicular cyst and only a partial oophorectomy was performed. One girl, age 11 yrs., with a fimbrial cyst of the right ovary, had had a previous oophorectomy on the opposite side 5 yrs. before the present admission.

Course: The postoperative course was uneventful in all 14 patients. It has been possible to follow the subsequent courses of only 8 of the patients. Four are living 9 to 11 yrs. from the date their illness began. The tumors in these patients were 2 dermoid cysts, 1 fimbrial cyst and 1 malignant teratoma. A 5th patient who had a dermoid cyst is alive and well 10 mos. postoperatively. Two girls with carcinomas and 1 with adenosarcoma died less than 7 mos. from the onset of their symptoms.

DISCUSSION

The variety of ovarian tumor most frequently found during childhood is the cyst. The simple and multilocular cysts constituted 32%, the dermoid cysts 24% of the ovarian neoplasms in the Witzberger and Agerty series. Sarcomas, carcinomas and teratomas

comprised most of the remainder. The granulosa cell tumor and the dysgerminoma apparently are of unusual occurrence in the child.

Children suffering from such tumors often present striking clinical findings and these neoplasms have therefore become well known despite their infrequency.

Granulosa cell tumors produce dramatic physical alterations and differentiation from other tumors causing somatic changes is therefore necessary. Bland and Goldstein[4] found 18 instances of granulosa cell tumor in children under 14 years of age among 150 cases of this neoplasm which had been reported up to 1935. Gross[5] and Harms[6] have also described cases of this tumor occurring in childhood. The findings which have been described in patients with granulosa cell tumor are: advanced body growth, lower abdominal or pelvic mass, hypertrophy of the breasts, enlarged nipples and labia, precocious menses and great increase in estrogen excretion. Similar physical alterations of premature puberty may occur in the juvenile female affected by a tumor of the third ventricle. In this disorder, however, there is no abdominal or pelvic tumor, the bone age is generally advanced, there is less estrogen excess and there may be alterations in water balance producing polyuria and oliguria. Signs of intracranial hypertension may also be found. Following the removal of a granulosa cell tumor the prognosis appears to be good for at least three years. Cases in which the follow-up period equaled 10 or more years have not been reported.

Arrhenoblastoma: Foderl[7] reported a case of this masculinizing tumor in a young girl, the first signs occurring at the age of 15 years. No patients younger than this, affected by arrhenoblastoma, have been found mentioned in the literature.

Dysgerminoma: A considerable interest in this tumor has existed due not so much to its frequency during childhood, but because of its occasional association with pseudohermaphroditism. Novak and Gray[8] found three patients less than 15 years of age in a series of 17 cases of dysgerminoma. Several of their patients with dysgerminoma were apparently feminine in character and menstruated regularly. Some of the affected adults had born children.

To the clinician there are several considerations of importance in the management of children with ovarian tumors: Ovarian tumors may occur at any age, even infancy. The symptoms produced are frequently minimal, even after the tumors have attained a considerable size. Irrespective of the benign character of many of them they are a potential danger to the patient and treatment should therefore be prompt surgical removal. Preoperative irradiation should only be considered in the event of the presence of metastasis.

Summary

Data on 14 cases of ovarian tumors occurring in children have been discussed in this presentation.

Ovarian neoplasm is uncommon during childhood. It should be considered however in the differential diagnosis of several conditions observed not infrequently by the clinician in girls from infancy through adolescence. These conditions are: lower abdominal pain of acute, subacute or chronic nature; abdominal or pelvic masses; precocious puberty and vaginal bleeding.

The treatment is surgical.

The prognosis in the malignant varieties is usually serious, but there are exceptions to this generalization. The prognosis in the benign types is good.

ACKNOWLEDGMENT

Acknowledgment is made to the following physicians for permission to include their cases in this series: Dr. Edward Donovan (Case 6); Dr. Bernard Hannan (Case 9); Dr. Paul Morton (Case 12).

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SPANISH ABSTRACT

Tumóres del Ovario en la Niñez

Los siguientes datos hacen referencia a catorce casos de tumores del ovario en niñas de diferentes edades asi: la paciente mas joven tenia solamente un ano y la mayor catorce.

El diagnostico anatomico de estos tumores fue asi:

Quistes dermoides	5
Quistes foliculares	2
Quistes fimbriales	1
Quistes para-ovarianos	1
Quistes peseudo-mucoides	1
Teratomas malignos	1
Adeno-carcinoma embrional	1
Corio-carcinoma	1
Adeno-carcinoma mesofrenico	1

Los neoplasmas del ovario no son comunes en la niñez. En el diagnostico diferencial debe considerarse sin embargo varias condiciones no observadas muy frecuentemente por los clinicos en niñas desde la infancia hasta la adolescencia. Estas condiciones son: dolor agudo en la parte baja de la region abdominal otras veces es sub-agudo o de naturaleza cronica; dolores abdominales o pelvianos similares a colicos menstruales; pubertad precos y hemorragia vaginal.

El tratamiento es quirurgico.

El prognostico en las variedades malignas es usualmente muy serio pero hay algunas excepciones a esta regla. En los casos benignos desde luego el pronostico es bueno.

119 East 84th Street

HUMAN EQUINE ENCEPHALOMYELITIS IN SASKATCHEWAN IN 1947

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AN EPIDEMIC of human equine encephalomyelitis, appearing in Saskatchewan in August 1947, and its relationship to an epidemic of this disease among horses, occurring at the same time in this district, is presented in this report. This relationship between the human and equine disease had been first suggested as early as 1932 by Meyer.[1] He reported two cases of what he considered had been human equine encephalomyelitis, suggesting a suspicious connection with the horse disease prevalent in California in 1930 and 1931.

There had occurred, here in Saskatchewan, prior to 1938, several puzzling cases of an unclassified neurologic disease, proved to be neither acute poliomyelitis nor encephalomyelitis of the von Economo type and, in retrospect, these too may be theorized to have been cases of equine encephalomyelitis. One patient was admitted to Regina General Hospital in April 1937 with "paralysis left side, possible infantile paralysis." Notes extracted from her chart mentioned that "on examination her whole left side was spastic, the tendo achillis was contracted and her fingers were clenched into her palm. There was considerable neck rigidity and cerebral irritability. Her spinal fluid cell count was thirty cmm., pressure normal." The diagnosis was changed to encephalitis. She died a few years later.

An epidemic of human and equine encephalomyelitis appeared in southern Saskatchewan in the late summer of 1938.[2,3] The equine epidemic resulted in the death of 15,000 horses. About the same time, there were 29 cases of human equine encephalomyelitis with their highest incidence between August 15 and August 25, the first case being reported July 20. Four patients died; 18 recovered completely; seven recovered partially. The youngest case was two months and the oldest, 72 years. The following was abstracted from the autopsy report on one of these cases: "Microscopic sections taken at all levels through central nervous system showed evidence of recent nonsuppurative inflammation. Cuffing of small vessels with lymphocytes was seen in both cerebrum and spinal cord and there was a patchy infiltration throughout with lymphocytes. Many of the motor neurons in cortex and cord were seen to be degenerating. The disease process appeared to be an acute encephalitis or polioencephalitis."

Coincident with the epidemic, there occurred in Massachusetts an epizootic of equine encephalomyelitis. Fothergill and his associates[4] reported that the virus of the Eastern type of equine encephalomyelitis had been isolated and identified as the etiologic agent in a fatal case of encephalitis. Feemster[5] reported that eight cases of human encephalitis had been proved due to the virus of Eastern equine encephalomyelitis, with a high fatality, 25 of the 38 cases under investigation having died. Here was a remarkable coincidence in that two diseases identical clinically, except for severity, and separated by

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half a continent appeared simultaneously but were shown to have been caused by a virus serologically different.[6] Antibodies produced in a case of the Eastern equine encephalomyelitis would not neutralize the virus of the Western type. During the outbreak of 1938 the author suggested the possibility that the human disease was due to the

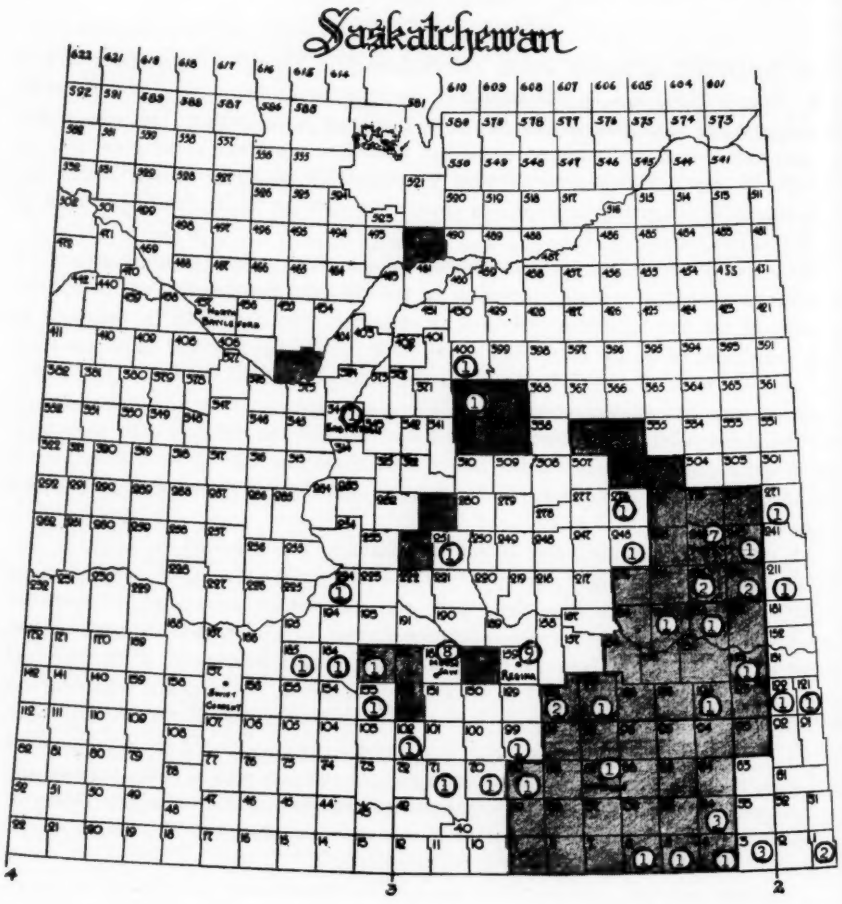

CHART I

Encephalitis—1947
Total—68 human cases
Shaded areas indicate presence of encephalomyelitis among horses.

equine virus and suggested an attempt be made to isolate any virus which might be present. Arrangements were made towards this end, but at that time the epidemic subsided and no further material was available. Although the disease was not at all prevalent in 1939, Fulton succeeded in isolating the Western equine virus on two occasions that year, one from blood and the other from brain tissue.

In 1942, Dr. D. F. Moore, Director of Pathology, St. Paul's Hospital, Saskatoon, Saskatchewan, reported on 238 out of 533 cases of human equine encephalomyelitis which appeared in the 1941 epidemic in Saskatchewan. Of these cases, the author attended 17 infants and at this date 12 are completely recovered and five have postencephalitic sequelae. There were similar epidemics in the same year in North Dakota, Minnesota and Manitoba—in all, 2792 cases, with a death rate of 12.4%. In a report of the Manitoba epidemic, Medovy[7] presented 19 cases in infants; nine recovered completely, two died, six presented sequelae and two were untraced.

Of the Saskatchewan cases of this 1941 epidemic, 162 cases were hospitalized in Regina and 116 of these received a total of 2,780 cc. of immune horse serum. There were 17 deaths from this series; five of these patients received no serum, five received it when moribund and seven received varying amounts from 10 to 150 cc. early enough to help if serum might have been of value. No decision could be made as to the value of immune horse serum from the series. The serum used was prepared by Fulton by hyperimmunizing several horses with the Western virus over a considerable period of time. Blood from the different animals was titrated against the equine virus in mice and embryos and the most potent one used in the treatment of the cases. The serum was found to be highly potent and capable of neutralizing several thousand minimum lethal doses. Experimental work done since that time would suggest that antiserum is not of any great value.

TABLE I

EIGHT CASES OF EQUINE ENCEPHALOMYELITIS—WESTERN TYPE

Name	Age Mos.	Sex	Date of onset	Temp. at onset	Font.	W.B.C.	SP. C.C.	Convs.	R.M. Lab.	U. of S.	Results
L.S.	3	F	Aug. 8	39.6	Norm.	17050	22	+++	Pos.	Pos.	Normal
T.F.	9	M	Aug. 10	40.0	Norm.	17750	90	++	Pos.	Pos.	Normal
B.S.	5	M	Aug. 5	39.5	+++		39	0	Pos.	Pos.	Normal
L.S.	1	F	Aug. 13	40.0	++	23800	295	+++	Pos.	Pos.	Mental retardation
Y.K.	3	F	Aug. 3	40.1	+++	31000	500	+++	Pos.	Pos.	Normal
M.P.	6	F	Aug. 4	40.2	+++	24200	200	+	Pos.	Pos.	Normal
H.P.	1¼	M	Aug. 4	39.5	++	21500	75	++	Pos.	Pos.	Paralysis of leg
C.P.	2	F	Aug. 5	40.1	++	12150	92	++	Pos.	Pos.	Normal

This presentation concerns the epidemic in southern Saskatchewan in August 1947. Sixty-eight cases of human equine encephalomyelitis of all ages were tabulated and these conformed geographically to the epidemic among horses in southeast Saskatchewan (Chart I). Of these 68 cases, 15 were under supervision in the hospital and of these eight are herein reported (Table I). The diagnosis has been confirmed by neutralization tests at the Rocky Mountain Laboratory and the Laboratory of Animal Diseases at the University of Saskatchewan. These cases had their onset from August 3 to August 13, inclusive; five cases came from Regina, three from points south and east. Five were

female, three male; the youngest was one month, the oldest nine; four were breast fed, four bottle fed. The clinical picture was almost identical with the cases reported by Medovy and those seen by the author in 1941 and was, briefly, as follows: onset was acute with temperatures ranging from 39.4 to 40.9°C. and subsiding from the third to fifth day of illness. During this febrile period nearly all the patients had recurring convulsions with muscular twitching and rigidity of limbs and tense to bulging fontanels. Every

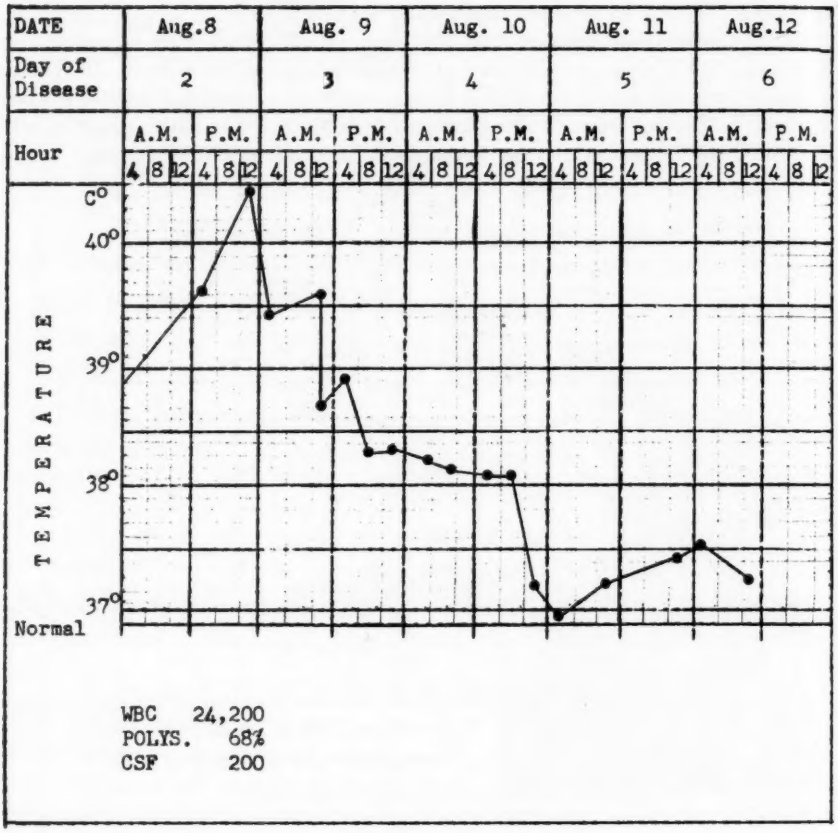

CHART II
Temperature chart of typical patient.

patient had an increased spinal fluid cell count, the lowest 22/cmm. and the highest 500/cmm. Analysis of spinal fluid revealed reducing bodies and chlorides normal and proteins in most instances somewhat above normal levels. All cases showed some pleocytosis, the highest having been 34,000 cmm., polymorphonuclears predominating. Some cases exhibited vomiting, others constipation; some were pale, others cyanosed. With one exception, at about the fourth to fifth day these symptoms subsided and the infants took on a normal appearance. Chart II is the temperature chart of a typical patient. This

child, one of female twins living in a two-room war-time home under good hygienic surroundings, was quite ill, with high temperature and bulging fontanel. Her twin sister lay on the same bed, smiling and apparently normal. Other reports indicate that two cases have been reported from the same family only rarely and suggests that some accidental vector, such as an insect, transmits the disease rather than its being developed by contact. Blood from the well baby was later found negative for neutralizing bodies. At the present date all cases appear normal with the exception of two, one of which exhibits microcephaly, spasticity and strabismus. This child was said to have been normal before the onset of the illness at the age of one month. The other child has some spasm in one leg but is mentally normal. Five other cases (S. G., L. McM., S. B., D. F., all under three months of age, and E. H., eight years) were reported positive from only one of the laboratories and are not included in the series although they presented a similar clinical picture.

Coincident with this epidemic of human equine encephalomyelitis, there was another of acute poliomyelitis (275 cases) and a few other cases of an unidentified encephalitis.

Infant B., aged 10 months, presented the following picture: in August 1947, the mother noticed this baby, then five months old, losing control of the head and having peculiar transient "spells." Examination at the age of eight months revealed this child probably mentally retarded and blood was positive for equine encephalomyelitis. In February 1948, Infant S. was diagnosed as having had encephalomyelitis in August 1947. The following was noted: "Probably mentally retarded; has spells of petit mal nature." In this case also, a blood neutralization test was returned positive. The deduction may be made that there were other cases of infantile human equine encephalomyelitis in Saskatchewan in 1947 than are herein reported and that others will turn up, presenting brain damage from this disease. It now seems advisable that all children presenting an abnormal mental state of an obscure nature have their blood checked against the virus of equine encephalomyelitis.

It should be realized that neutralization tests have definite limitations and, unless certain facts are borne in mind, results may be confusing. Although it has been shown that few people in Saskatchewan naturally harbor neutralizing bodies for the equine virus, it is the practice during an outbreak to secure a blood sample immediately the disease is suspected and a second sample in from 10 to 15 days. A negative reaction with the first and a positive with the second specimen is, of course, taken as proof of infection with the equine virus. When dealing with infants of a few months, the first test may be eliminated, accepting a positive reaction a short time after the illness as indicative of the equine disease. It is more difficult to appraise the significance of the results obtained when the test is in an endeavour to determine if a patient's present condition could be a sequel to a previous infection. In such cases a number of factors must be considered, such as medical history, length of time elapsing between illness which may have been due to the virus of equine encephalomyelitis, and whether the patient had been resident in a district where an outbreak of the disease had occurred even though there was no evidence of a severe illness at that time. It has been found that in the majority of cases where a positive reaction is obtained with this class of patient, there is usually a history of an illness which had been definitely diagnosed as equine encephalomyelitis or suspected of having been due to the equine virus. When negative reactions are secured with patients having a history of a possible previous infection, the length of time between

the sickness and the conducting of the test must, of course, be taken into consideration, since neutralizing bodies do not remain in the blood indefinitely and the period of time in which they can be detected is variable in different individuals.

Summary

Eight cases of infants with human equine encephalomyelitis confirmed by neutralization tests have been presented, six having recovered completely and two left with residua, one mentally deficient.

Because six months later two additional patients who had abnormal mentality of an obscure nature, a suggestive clinical history and a positive neutralization test were considered to have had human equine encephalomyelitis in this epidemic, it would appear advisable to check the blood of all children with abnormal mentality of an obscure nature against the virus equine encephalomyelitis.

Acknowledgment

Acknowledgment is made of assistance from the personnel of the Rocky Mountain Laboratory at Hamilton, Mont., in particular, Dr. R. R. Parker and Dr. Carl M. Eklund, and also from Dr. J. S. Fulton of the University of Saskatchewan; Dr. H. S. Doyle, Epidemiologist for the Province of Saskatchewan, and Mrs. Mildred Quayle.

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Spanish Abstract

Encéfalomielitis Equina Humana en Saskatchewan in 1947

La relación entre la encéfalomielitis humana y equina, reportada por primera vez en California en 1932, se presenta en un relato de la epidemia de 1947 en Saskatchewan. También se hace referencia a las epidemias de 1937 y 1941 en Saskatchewan. La primera apareció simultaneamente con una epidemia en Massachusetts y se encontró idéntica clinicamente, aunque menos virulenta; pero se probó que era diferente serologicamente. El valor del ensayo de neutralización en la diagnosis ha sido confirmado.

Se han presentado ocho casos de niños con encéfalomielitis equina humana confirmada por ensayos de neutralización, seis se restablecieron completamente y dos quedaron con residuos, uno deficiente mentalmente.

Debido a que seis meses después se presentaron dos casos más con mentalidad anormal de una naturaleza oscura y a causa de una historia clínica sugestiva y un ensayo de neutralización positivo, se consideró que ellos habían tenido encéfalomielitis equina humana en esta epidemia. Se cree conveniente examinar la sangre de todos los niños con mentalidad anormal de una naturaleza oscura contra el virus de la encéfalomielitis equina.

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ELECTROENCEPHALOGRAPHY IN CHILD NEUROLOGY AND PSYCHIATRY

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THE past 10 years have produced scores of electroencephalographic studies in children describing a variety of abnormal waves. Those with severe brain lesions or diseases, paroxysmal disorders of function, and mental and behavior disorders have received more or less extensive study. To many pediatricians the significance of much of this work must be hard to evaluate. The interpretation of the EEG showing various odd shapes and complexes of waves at different frequencies, and the methods used to locate the origin of these abnormal discharges, may appear bewildering even to those who have had the opportunity of studying it more intensively. It must be recognized that, in the EEG, waves represent a dynamic function of the brain as opposed to the demonstration of structural alterations shown in the pneumoencephalogram. Consequently, the results obtained may depend upon the transitory conditions of the patient at the time of the examination.

GROWTH AND INTELLIGENCE

Electroencephalograms in infants and young children are more difficult of interpretation due to the normal changes in brain wave patterns with age, and due to greater instability of these patterns.[1-7] The greater instability of brain waves in childhood has been clearly demonstrated in studies of the effects of hyperventilation at different ages and of effects of head injuries.[8-14] Only the motor regions show a regular pattern of electrical activity at birth (and before, according to Lindsley,[15] who has recorded an EEG through the abdominal wall of a pregnant woman). Parieto-occipital regions become organized into a slow alpha rhythm between three and six months of age. These initially slow and often irregular rhythms obtained during the first year would be considered definitely abnormal in a child a few years older. This is illustrated in the records of two children (Fig. 1), both eight years of age. In the one who developed in a relatively normal manner there is shown a marked change in his EEG taken at one year of age as compared to that taken at eight years. In the other, who was mentally deficient, his record at the age of eight closely resembled that of the former child at one year.

Although there is considerable variation shown between different children of the same age, a given child will show little variation in EEG from day to day, unless due to some intercurrent trauma or disease.[16,17] The increase in alpha frequency with age approximates a logarithmic curve as do many growth processes (Table 1).[18]

Bernhard and Skoglund[18] found that the rapidity of response to visual stimulation (the alpha blocking time) bears a close relationship to the frequency of the alpha

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rhythm. They suggest that the speed of certain mental processes may therefore be related to the frequency of the alpha rhythm.

Contrary to what might be expected from the above relationships shown between the

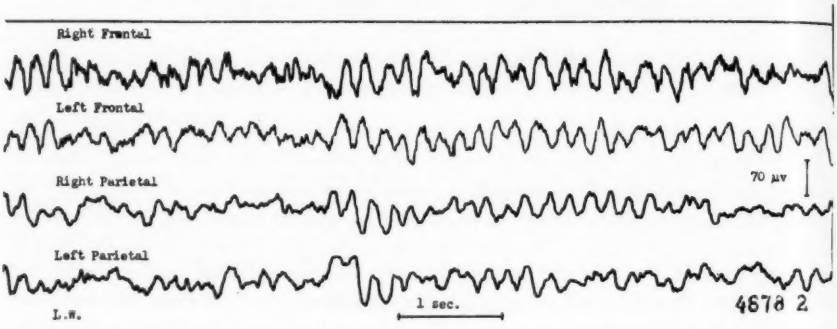

FIG. 1a. EEG of mentally defective 8 yr. old boy shows predominant frequencies of about 5/sec.

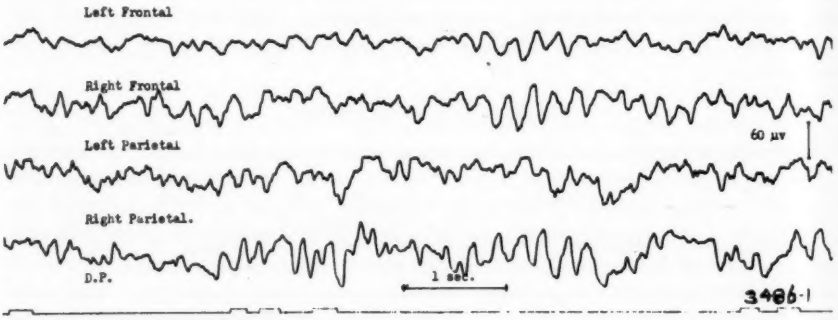

FIG. 1b. shows predominant frequencies of about 5/sec. in 1 yr. old child of average intelligence.

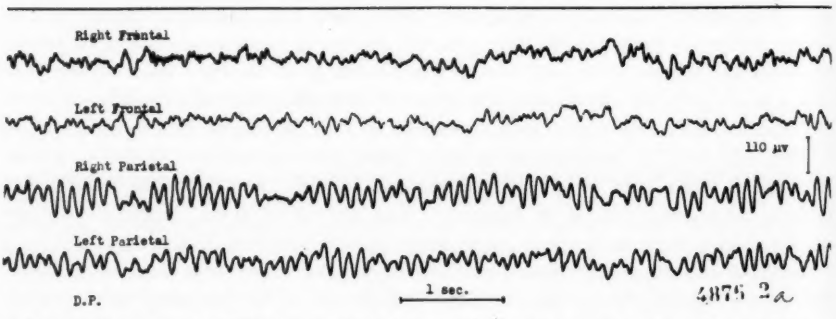

FIG. 1c. shows sample EEG of same child at 8 yrs. of age with normal alpha rhythm at 9/sec.

maturation of the brain and changes in the EEG, there is not a close correlation between the EEG and intelligence, as measured by the usual intelligence tests. Numerous studies[19–23] of mentally deficient and normal children have shown that the varied

and complex factors causing mental deficiency may cause various forms of disturbances in the EEG, none of which bears a simple relationship to general intelligence. The simple rhythmic and random waves that can be recorded represent an extremely crude picture of only certain large mass discharges of cortical neurones. The finer detail of the integrative activity of the brain which might be related to such complex functions as personality and intelligence could hardly be expected to reveal itself in such a crude oversimplified manner.

Heredity

Hereditary determinants of certain abnormal and normal brain wave patterns have now been thoroughly established.[24–29] The early studies showing similar records in identical twins have been confirmed, with the additional observation that one of a pair of twins tends to have more alpha waves from the right hemisphere, while his brother has more from the left. This is an electroencephalographic manifestation of reversed lateral

TABLE 1*

Age	No. of cases	Mean freq./sec.	Range/sec.
4–11 mos.	17	5.3±0.2	3.5– 6.6
1– 2 yrs.	23	6.5±0.1	5.5– 7.4
3– 4 "	20	7.4±0.1	6.2– 8.9
5– 6 "	21	8.3±0.1	7.5– 9.2
7– 8 "	23	8.5±0.1	7.5–10.3
9–10 "	21	8.8±0.1	7.5–10.2
11–12 "	18	9.3±0.2	8.4–10.4
13–14 "	17	9.3±0.2	8.3–11.0
15–18 "	17	9.5±0.2	8.2–11.1
19–30 "	23	10.2±0.1	9.0–11.0

* From Bernhard, C. G., and Skoglund, C. R., On alpha frequency of human brain potentials as function of age, Skandinav. Arch. f. Physiol. **82**: 178, 1939.

cerebral dominance in identical twins, the one naturally right handed, and the other left handed.[30]

The well known studies of Lennox and Gibbs have established an hereditary factor in the dysrhythmias of idiopathic epilepsy. The more recent studies of Lennox and the observations of other workers, particularly those of Bridge,[31] have shown that hereditary predisposition may not be as important as the earlier studies would lead one to believe. Lennox's suggestion that hereditary predisposition may play an important role in the incidence of convulsions following trauma or infectious disease has received some confirmation in the studies of Cook,[23] although studies of the parents of patients with symptomatic epilepsy have shown that other factors are probably more important in most of these cases.

Studies of the EEG in families of children with Sydenham's chorea produced evidence for an hereditary predisposition in certain instances.[32] Some of these patterns resembled those in relatives of epileptic patients, demonstrating some nonspecificity in hereditary determinants of cerebral dysrhythmia.

More recently Knott and coworkers[33,34] have shown that electrocardiographic abnormalities may be found in a fairly high proportion of the parents of patients with primary behavior disorders and psychopathic personality.[28]

Genetic defects may therefore manifest themselves in different forms of malfunction and in various types of alteration in the electrical rhythms of the brain. A clear history of familial disease or EEG of the parents is necessary, however, in order to thoroughly establish a genetic factor in most instances, since the forms of disturbances in the EEG may be closely simulated by abnormalities of intrauterine development, injuries or anoxia at birth, encephalopathies of toxic, metabolic or infectious origin, and severe head injury. When a clearly localized abnormality appears in the EEG, however, without generalized changes as well, hereditary predisposition may be ruled out with reasonable assurance.

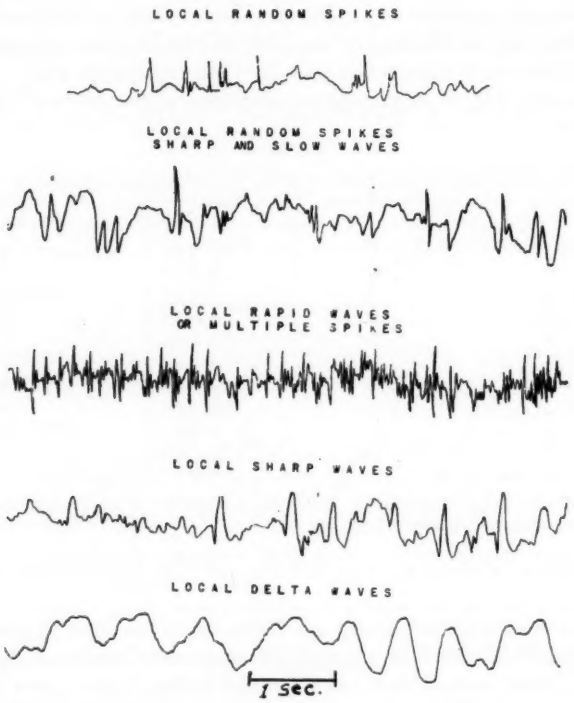

FIG. 2. Electroencephalographic patterns from local areas of cortex in patients with focal epileptogenic lesions.

CONVULSIVE DISORDERS

Epileptiform disturbances of neuronal function are characterized by episodic excessive synchronized neuronal discharge of small or large aggregates of nerve cells and circuits. These discharges differ from those normally occurring in these cells and circuits chiefly by the fact that larger numbers of units are synchronized into a single beat, a feature which has been termed *hypersynchrony*. In addition certain groups of neurons appear to be sensitized to spontaneous autonomous excessive discharge, or they may respond excessively to incoming afferent impulses as in "reflex epilepsy."

This spontaneous or induced local discharge may occur at random intervals from a

small cortical area with slight or no obvious clinical disturbance in the patient. It is detected in the EEG by the appearance of random spikes or sharp waves which protrude from the background of more or less smooth rhythmic activity (see Fig. 2). The onset of a clinical seizure is heralded by a gradual increase in the voltage and number of initially arrhythmic spikes until they become organized into rapid rhythmic activity recruiting adjacent neurones and then distant neurones in the evolution of the generalized seizure (Fig. 3). With this recruitment and spread, rhythmic discharge develops.

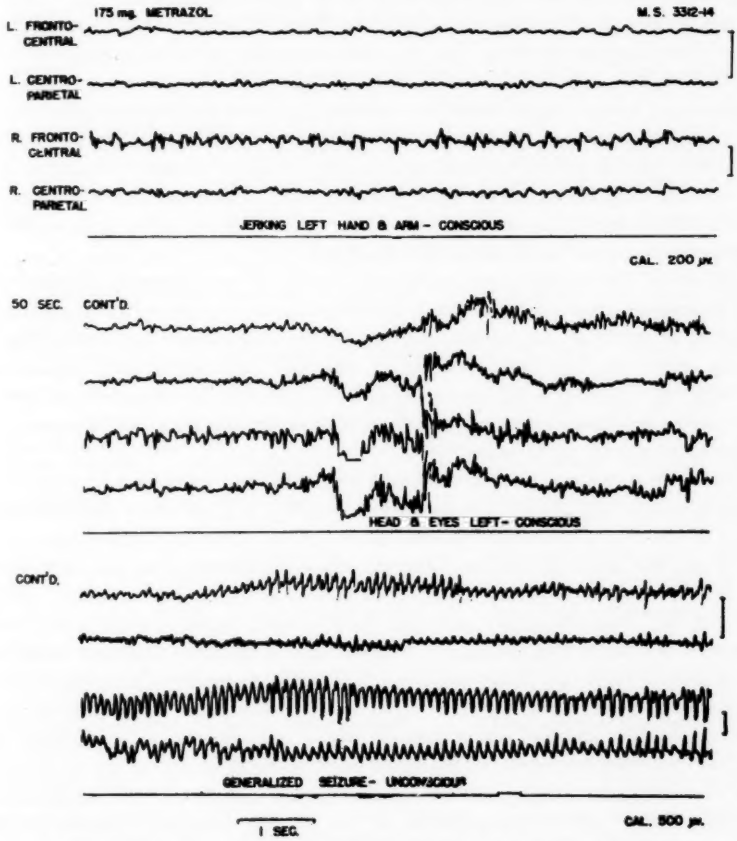

FIG. 3. EEG during onset of focal seizure starting in right precentral arm area. Seizure progressed to become generalized convulsion.

The rhythm itself may manifest itself in a wide range of frequencies, from 1 or 2, to 30 or 40/sec., including those frequencies which are usually considered normal when of lower voltage. Consequently epileptic discharge may or may not be initially a "dysrhythmia," though abnormal frequencies are common. The more rapid frequencies characterize cortical seizures recorded at their source of onset. Slower frequencies usually imply a disturbance conducted from a distance, and frequently involving thalamocortical, or other "long circuit" multineuronal reverberating circuits. The transition from a rapid

spike form of 10 to 20 milliseconds duration recorded directly at the source of an epileptic focus to a sharp wave of 50 to 100 milliseconds duration can be achieved merely by conduction through synapse to a distance. If the spikes are buried in some deep-seated part of the brain, inaccessible to electroencephalography, only the longer waves, or rhythmic waves may appear from electrodes on the outside of the head.[35, 36] Consequently, slower waves or frequencies may not mean a different kind of epilepsy, but merely a different localization of onset. A series of rhythmic slow waves can be produced in the cortex by a single brief electrical stimulus to the thalamus in animal experiments.[37]

When a child is the victim of a convulsive disorder with repeated seizures, the following questions come to mind. Has this child idiopathic or essential epilepsy with the possible hereditary implications that go with it? Are his seizures the result of some form of generalized encephalopathy due to a metabolic disorder such as hypoglycemia, or to some degenerative disease of the brain? Are they due to some local lesion of the brain, either from birth or following head injury or local vascular accident? Or are we to suspect an expanding lesion of the brain such as tumor or abscess? The EEG may be of genuine help in answering these questions. The question of idiopathic epilepsy and generalized organic brain disease can be considered first.

Examples of the principal types of disorder found in true idiopathic epilepsy, as opposed to seizures arising from diffuse encephalopathy, are shown in Fig. 4. The frequent occurrence of petit mal and grand mal seizures in the same patient, and the fact that most patients with wave and spike patterns in the EEG have grand mal seizures, show that these two forms of idiopathic epilepsy have a common physiopathologic basis, the one a minor, and the other a major seizure, both starting with a loss of consciousness and both "petit mal" at the onset.[36, 38]

Working in a neurosurgical environment, Penfield[39] and the author have approached the whole problem of the EEG in convulsive disorders in a somewhat different manner. Simply to classify the epilepsies into four or five groups according to the pattern of their brain waves has not been sufficient. The electrographic pattern alone has been found to be a rather unreliable guide to the form of clinical seizure.[40] The familiar "spike and dome pattern" does not signify petit mal epilepsy when recorded from a focal area of damaged brain. Rapid rhythms do not always indicate a diagnosis of grand mal epilepsy; they may arise from the vicinity of a calcified lesion or tumor causing focal epilepsy. The so-called square-topped waves, or 6 per second rhythms, are found in many patients without convulsive disorder, or in patients whose seizures bear no resemblance to the so-called "psychomotor attack." They often point to focal lesions of the brain. It is in terms of cerebral localization, the neuronal units and circuits activated in the epileptic discharge, that a rational interpretation of the EEG in relation to clinical manifestations is gradually becoming clarified.

Etiologic factors are not given a secondary role in this conception. This first step to an understanding of etiology should be the determination of the site of disease. In the convulsive disorders this is achieved, to a degree, by careful observation of the pattern of onset and spread of the clinical seizure, and by detailed localization studies with the EEG. Structural changes of significance often appear in the pneumoencephalogram. Finally, in selected cases, it is possible to verify the actual site of onset of epileptic discharge by observations made directly on the exposed brain during neurosurgical procedures designed to remove that portion of the brain which is the "trigger zone" of epileptic discharge. At this time, local electrical stimulation combined with the electro-

TABLE II

CONVULSIVE DISORDERS

Clinical	EEG	
Type of Seizure	Localization	Form
Idiopathic Epilepsy		
Petit mal	Bilaterally synchronous (diencephalic, probably thalamic)	Rhythmic 3/sec. wave and spike (Fig. 4,* first two lines.)
Myoclonic	Bilaterally synchronous (diencephalic, thalamic?)	Short bursts, multiple spike and wave (Fig. 5.)
Petit mal and grand mal	Bilaterally synchronous (thalamo-cortical?)	Rhythmic spike and wave with multiple spikes
Grand mal	Diffuse generalized (predominantly cortical?)	Rapid rhythms (Fig. 4, second two lines.)
Cerebral Seizures, Unlocalized (with known organic brain disease)		
Major generalized convulsions	Diffuse or multiple foci (cortical)	Random irregular, slow, sharp or rapid (Fig. 4, last two lines.)
" " "	Bilaterally synchronous	Rhythmic 2–6/sec. sharp or slow, some 7–20/sec.
Myoclonic	Bilaterally synchronous (subcortical?)	Short bursts of multiple spike and wave (Fig. 5.)
Minor lapse of consciousness (like petit mal)	Bilaterally synchronous (subcortical?)	Rhythmic sharp and slow waves at 1–2.5/sec. (Fig. 6.**)
Episodic confusional states and behavior disorders	Bilaterally synchronous	Dysrhythmias of various forms, usually slower frequencies
Focal Cerebral Seizures		
Somato-sensory or motor (Jacksonian)	Pre- or post-central gyrus	Local random spikes or sharp waves
Masticatory	Anterior Sylvian region	Local random sharp waves with bilateral 2–6/sec. rhythms
Simple adversive (conscious turning of head and eyes)	Mid-frontal cortex	Local random spikes or sharp waves
Unconscious adversive	Anterior frontal	Local random spikes or sharp waves
Tonic postural	Subcortical, brain stem	Generalized slow
Visual	Occipital cortex	Local random spikes or sharp waves
Olfactory	Uncinate gyrus	Bitemporal or basal sharp waves, 4–6/sec. rhythms. Local spikes at operation
Gustatory	Anterior Sylvian region	Local random sharp waves and bilateral 2–6/sec.
Autonomic-diencephalic	Region of 3rd ventricle	Basal slow or sharp with some bifrontal dysrhythmia
Autonomic-cortical	Orbital or mesial frontal, island of Reil, etc.	Local sharp and bilateral 2–6/sec. waves
Hallucinations and illusions	Temporal and parietal	Local spikes or sharp waves
Forced thinking	Frontal	Local spikes or sharp waves
Aphasia	Frontal, temporal or parietal	Local spikes or sharp waves
Behavior automatisms ("psychomotor")	Anterior deep temporal	Local sharp waves and temporal 2–6/sec. rhythms
Confusional states with automatic or stereotyped behavior	Frontal or fronto-temporal some with subcortical involvement	Local sharp waves or bilateral 2–6/sec. rhythms

* One patient may show both spike and wave form and rapid waves at different times or the spike and wave may merge into the rapid waves as a petit mal seizure progresses to grand mal.

** The sample EEG shown in Fig. 6 is that of a boy aged 10 yrs. who has had minor seizures and occasional major seizures for 6 yrs. and was thought to have had idiopathic epilepsy. During the past 2 yrs. he has developed paroxysmal abdominal pain and vomiting. He has a low white cell count and eosinophilia; is allergic to milk, peas, beans and wheat; has only rare minor attacks if kept on a wheat-free, milk-free diet. Gastro-intestinal symptoms have completely cleared with dietary control.

corticogram makes it possible, in many instances, to discover more accurately the diseased area of brain. If it is sufficiently discrete, and can be removed without too great impairment of important functions (such as speech and movements) the seizures may be arrested.

From these experiences over the past 10 years, from studies of the pattern of clinical seizure in relation to the EEG in several thousand patients, and from direct observations from the exposed brain in over 200 patients, a working classification of the convulsive

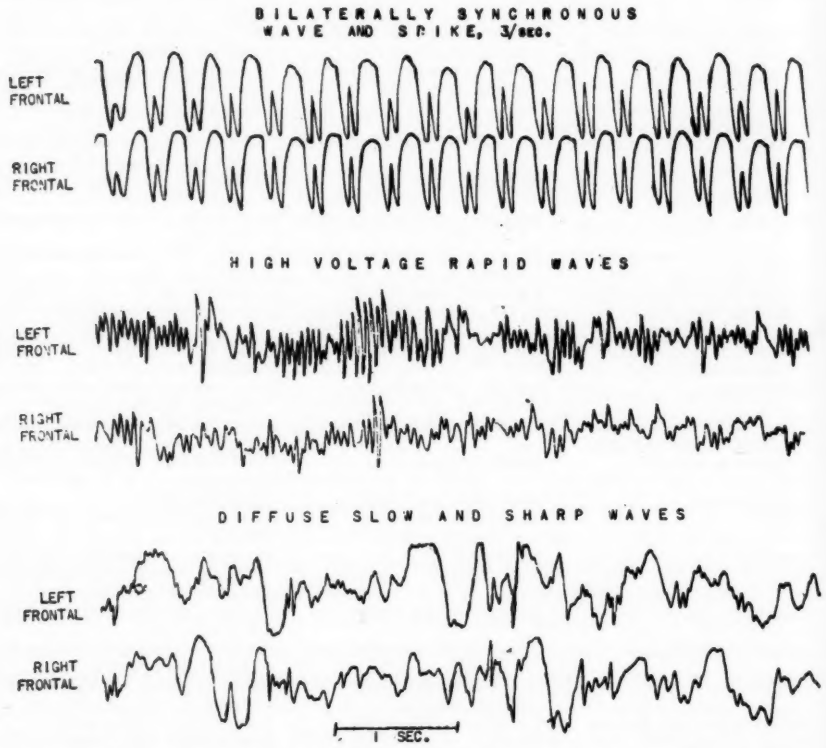

FIG. 4. First 4 lines illustrate principal types of EEG characteristics of patients with idiopathic epilepsy. Last two lines are from patient with generalized seizures but with diffuse encephalopathy, not idiopathic epilepsy.

disorders in relation to the EEG and pattern of clinical seizure has been developed. Its present form is undergoing continual revision as further experience is gained. (Table II, Figs. 4, 5 and 6.)

This outline illustrates some of the localized aspects of these disorders. Without this orientation, the clearly localized onset for epileptic seizures of many patients may be missed. More precise localization can usually be made than that suggested by Casamajor et al.[41] It requires detailed observation and extensive localization study to determine the focus of onset in many cases. Unless this is attempted many patients will be considered nonfocal when they should truly be classified with the focal epilepsies. In many the true

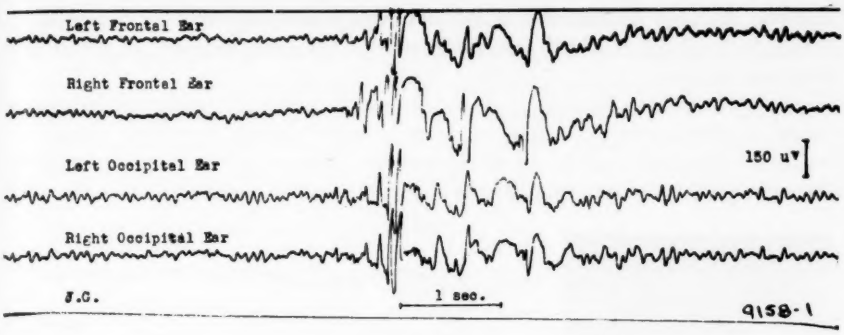

FIG. 5. Characteristic form of bilaterally synchronous discharges in myoclonic epilepsy. These may be either idiopathic or postencephalitic.

focus can only be surmised, in others not seen at all, in the usual EEG from scalp surface electrodes. It is then sometimes found when records are taken directly from the exposed cortex at operation (Fig. 7). In others, the site of onset or circuits primarily involved are still unavailable with the neurosurgical technic at our disposal. In others, epileptogenic areas are so numerous and widespread that surgical therapy is not possible. In many of these, other factors affecting brain metabolism and excitability must be sought after.

The great variety of form of epileptic seizure which may arise from onset in different parts of the brain is seldom fully appreciated. These various forms of seizure tend to reveal the functional characteristics of the particular part of the brain or circuits within the brain in which the epileptic disturbance is found to arise. Consequently, the form of seizure itself depends to a large extent upon what portion of the brain is initially involved and the path of its spread to other areas or circuits. In these studies about one third of the children examined with convulsive disorders must be classified as idiopathic in the present state of our ignorance. Another one third have generalized electroencephalographic disturbances probably due to organic brain disease, but without a clear localization of onset. Some of these may have a focus of onset in some deep-seated brain area inaccessible to the EEG. Finally, about one third have a fairly clear focus of

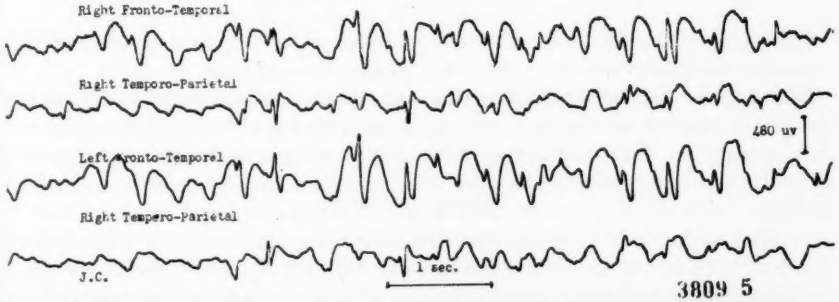

FIG. 6. Allergic encephalopathy with epilepsy. Diffuse slow and sharp waves with some bilaterally synchronous sharp-slow sequences at about 2-2.5/sec. are common in diffuse encephalopathies of various etiology. They should be clearly distinguished from EEG of idiopathic epilepsy.

epileptic discharge demonstrated in the EEG and usually supported by clinical examination.[42] In all cases a focal disturbance must be diligently searched for before it is definitely ruled out.

Febrile convulsions in children do not necessarily indicate a serious prognosis with regard to chronic convulsive disorder. Many of these patients show EEG within normal limits when well, and do not develop epilepsy. When a child responds repeatedly to the usual childhood diseases with convulsions, and there are positive electrocardiographic

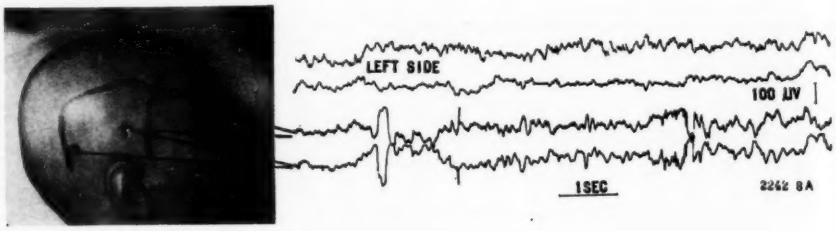

FIG. 7a.

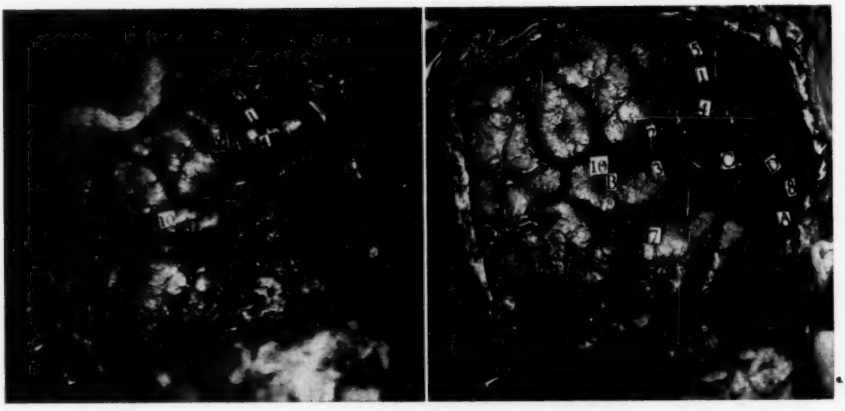

FIG. 7b.

findings between attacks, a latent convulsive disorder probably exists.[43] Prophylactic anticonvulsant medication should be used in these cases at times of stress.

One negative EEG in a patient suspected of epilepsy is not a certain indication that the patient may not have epileptic seizures. Even when hyperventilation is used to activate epileptiform discharge there are 5 to 10% of epileptic patients who may be in a particularly refractory stage at the time of the electrocardiographic examination. With additional methods of activation, such as by the administration of small amounts of metrazol (maximum of 6 mg./kg.) by slow intravenous injection, or by other methods (such as hydration, sleep, seconal and insulin) and with repeated examinations, latent epileptic disorders can be revealed in the EEG of nearly all patients with true epilepsy. The existence of paroxysmal electroencephalographic disturbances do not, however, always indicate clinical epilepsy.[44]

The Electrocardiogram and Medication

The type of disturbance in the EEG may serve as a guide to the selection of medication.[45,46] In general, those patterns characterized chiefly by slow rhythmic waves, usually at 3 to 6/sec., often bilaterally synchronous, respond better to dilantin, some to tridione, with perhaps some stimulant such as benzedrine or caffeine added. Phenobarbital and bromides seem less effective in patients with slow rhythms and may be actually contraindicated. These latter drugs are more effective in patients with rapid waves in the EEG, although these distinctions are not absolute.

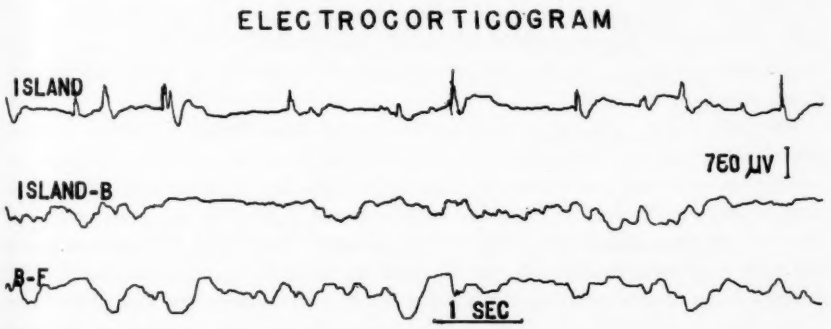

Fig. 7c.

Fig. 7. Focal epilepsy due to atrophic lesion of first temporal convolution and Island of Reil.* Preoperative EEG (Fig. 7a) shows focus of slow waves, sharp waves and occasional spikes from region of right sylvian fissure near point marked with cross. At operation (Fig. 7b), electrocorticograms taken from exposed cortex revealed sharp waves from first temporal convolution, as indicated by letters C and D, and few spikes from D. First temporal convolution appeared yellow and tough in consistency in its anterior portion extending within fissure of Sylvius. Electrical stimulation at point 8 and at C caused prolonged afterdischarge in electrocorticogram. Upon removal of anterior portion of temporal lobe as shown on right (Fig. 7b), recording electrodes were placed on Island of Reil and spikes shown in record (Fig. 7c) below were obtained. Consequently, cortex of Island was removed as well.

* This 10 yr. old girl began to have seizures at age of 2 yrs. She would have as many as five seizures per day which were first thought to be due to idiopathic epilepsy. She was admitted to hospital at age of 10 yrs. while in status epilepticus. After status was brought under control, it was found that her seizures began by a "pounding in heart" with sensations in epigastrium. This was followed by turning of head and eyes to left, twitching of left side of face and masticatory movements of mouth.

The EEG is not always a reliable guide to the clinical effectiveness of a given anticonvulsant treatment. Some patients will show marked clinical improvement without much change in the EEG; others may show change in the EEG with corresponding clinical improvement. In general, however, drugs which reduce the number of attacks also diminish the abnormality in the EEG.

The Encephalitides

The changes in cerebral function caused by acute encephalitis, whatever its cause, are reflected in pronounced disorganization and slowing of the brain waves.[47–49] Epileptiform discharges, often of a focal character, are observed in patients developing convulsive disorders. The persistence of pronounced electroencephalographic abnormality following the acute phase of the disease is correlated highly with the development of convul-

sions. Other postencephalitic disorders are not necessarily associated with marked changes in the EEG.

In the virus encephalitides, Shinners has found marked changes in the EEG, usually but not always associated with clinical signs of encephalitis. It has been found[50, 51] that poliomyelitis and polioencephalitis electroencephalographic changes are also common, especially in children under 12 years of age. During the acute stage of poliomyelitis, without apparent clinical signs of associated encephalitis, there may be definite electroencephalographic evidence for cerebral involvement as well, suggesting a degree of encephalitis in most cases. These acute disturbances may clear up within four to six months, suggesting that the cerebral changes may be largely resolved in many cases. In others abnormalities have been found to persist five to 10 years after the acute illness, but in these cases there may be also clinical evidence of changes in behavior or personality, or persistent convulsive disorders.

The EEG is not a reliable guide to the amount of brain damage following encephalitis. A patient may be hemiplegic, or he may show profound alterations in personality or intelligence with little residual modification in the EEG. On the other hand, severe local changes may be observed in the EEG in patients not presenting any gross neurologic signs or symptoms. This is due to the fact that cerebral tissue which has been completely destroyed is electrically silent, and the surrounding tissue may produce normal electrical rhythms, but a marked neurologic deficit may result from the destroyed area of the brain.

Abnormal brain waves arise from cerebral tissue which is functioning in an abnormal manner. If this tissue is in an area of the brain which does not give rise to gross neurologic signs, it may not reveal itself in the usual neurologic examination. However, persistent electroencephalographic abnormality following encephalitis is frequently related to behavior disorders or other neurologic signs apparent in the more detailed clinical examination. Such abnormalities should always be borne in mind as pointing to potential, if not actual, postencephalitic sequelae, especially in relation to the development of convulsive disorders.

Injuries and Anoxia at Birth

Lesions of the cerebral cortex following birth trauma or anoxia usually reveal themselves by a variety of alterations in the EEG. Irregular slow and sharp waves characterize areas of cortical atrophy. High voltage sharp waves and spikes usually point to a latent or manifest focus of epileptic discharge. An area of electrical silence often indicates a large porencephalic cyst,[52] or subdural hematoma. Bursts or rhythmic slow waves appearing bilaterally may point to a lesion of subcortical structures in the thalamus or basal ganglia. Lesions of the basal ganglia causing cerebral palsy, however, may occur without significant alterations in the EEG, especially in those without associated mental deficiency.

Head Injuries After Birth

Generalized severe electroencephalographic disturbances accompany cerebral concussion, but these may clear up in a few hours or days if the initial injury was mild.[14, 53] In more severe closed head injuries with associated cerebral contusion, it may require many months before the EEG approximates a normal picture, or abnormality may persist indefinitely. Consequently the EEG may aid in assessing the severity of injury and in following recovery progress (Fig. 8). With depressed skull fractures and cerebral

laceration, local electroencephalographic abnormalities may persist for years at the site of injury, and if spikes or sharp waves begin to appear a focus of epileptic discharge may be in the process of development. Here again it must be recalled that absent or dead brain does not produce brain waves so that if a good debridement of the damaged cortex has been carried out the EEG may return to normal, or nearly so.

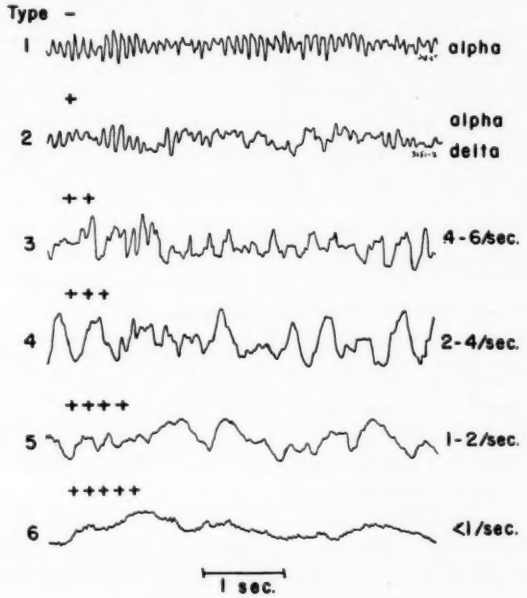

FIG. 8. Classification of degrees of abnormality in EEG following head trauma. First record is normal for child over 8 yrs. of age. In 5th and 6th lines are samples of records from brain which has been severely injured. Under 8 yrs. of age, variation due to age alone must be taken into consideration as well as type and amount of slow wave activity.

The EEG is not a reliable guide to the diagnosis of subdural hematoma, although in about 50% of such cases a relatively quiet area may suggest its presence.

BRAIN TUMOR AND ABSCESS

Superficial tumor or abscess of the cerebral hemispheres may be localized by the EEG by the presence of delta waves in their vicinity, or by relative electrical silence immediately over them. Local rapid waves are also occasionally recorded from cortex adjacent to a neoplasm. Deep-seated tumors affecting subcortical structures may remain undetected, or they may produce generalized changes in cortical rhythms. Subtentorial tumors are more difficult of localization but are often associated with slow waves in the occipital region, or over the posterior fossa. A left cerebellar lesion may cause a projected focus of delta waves in the right frontal region making differential localization difficult. Lesions of the midbrain and pons, especially if extending above the tentorium, may disturb the electrical rhythms of the entire cortex. But differential diagnosis of tumor versus trauma or local vascular disease cannot be made by a single electrogram.

Sydenham's Chorea

Slow waves and paroxysmal rhythmic disturbances at 4 to 6/sec. have been found in children with chorea. The remission and exacerbation of symptoms is related in some cases to concomitant improvement and deterioration in the EEG.[33, 54] Abnormalities are not found in the EEG of some mild cases of chorea, even when active clinically.

The form of dysrhythmia found in chorea is not specific for this disease. It is not localized to any specific brain area, although maximum disturbances are present in the milder cases from frontal and central regions. In hemichorea the maximum abnormality is found in the contralateral hemisphere. It seems to represent a diffuse disorganization of cerebral rhythms, possibly a reflection of disturbances in basal ganglia or diencephalic function as well as perhaps some primary cortical involvement, since Kennard[55] has shown that experimental lesions of the basal ganglia will produce disturbances in the EEG in monkeys.

Studies of siblings of patients developing chorea suggests that hereditary predisposition may be a factor in certain cases.

Behavior Disorders

Between 60 and 75% of children with severe behavior disorders have been shown to have definite abnormalities in the electrical rhythms of their brain.[56–72, 34] Certain of these disorders seem related to a constitutional defect of development, while others are the result of some form of encephalitis which had been previously unrecognized, or the sequel of head injury or a systemic metabolic disease affecting cerebral function. What does this mean in terms of treatment?

Certain of these patients have shown a good response to dilantin, especially when combined with benzedrine. Curiously, their behavior may show marked improvement without significant alteration in their brain waves. In spite of the indication of an organic substratum for the behavior difficulty in these cases, psychiatric treatment and intelligent management of the environment may help to adjust these children to their disability. Such adjustment may be unusually difficult, however, in cases with severely abnormal brain waves, for the adjusting mechanism itself may be out of order.

Summary

The principal applications of electroencephalography to child neurology, neurosurgery and psychiatry are as follows:

Abnormalities in the EEG of parents or siblings of patients with nervous or mental disease assists in evaluating possible hereditary factors.

Nervous and mental disorders caused by abnormalities of intrauterine development, injuries or anoxia at birth, encephalopathies of toxic, metabolic or infectious origin, and severe head injuries, may be reflected in abnormal brain waves in many but not all cases. In some, the location and type of cerebral pathology may allow marked changes in behavior, such as spastic paraplegia, with no significant alteration in the EEG.

The EEG gives little reliable information with regard to intelligence and the finer structure of personality.

Cerebral damage due to tumor, abscess, trauma or local vascular lesion may be localized by the EEG but pathologic diagnosis must be made from a careful history and other methods of clinical examination in most cases. With improved methods, deep-

seated lesions involving subcortical structures, as well as superficial lesions, may frequently be accurately localized by the EEG.

Subdural hematomata are not accurately diagnosed by the EEG in most cases.

The EEG is most useful in the epilepsies and convulsive disorders. Differential diagnosis between idiopathic epilepsy and symptomatic convulsive disorders can usually be made by the EEG except for certain postencephalitic conditions which may simulate the electroencephalographic patterns of the idiopathic or "genetic" epilepsies. The form of clinical seizure depends upon the brain area of onset of the epileptic discharge, and its path of spread. The form of electrical disturbance has no specific significance except as pointing to a certain localization of onset. A wide variety of seizures are caused by focal epileptic discharge arising primarily in various areas of the cortex. These may be localized by the EEG when on the convexity of the hemispheres, but may be missed when buried in fissures or on the ventral or mesial surfaces of the brain. They are frequently discovered only when electrodes are placed directly on the brain surface exposed at operation. Bifrontal rhythmic disturbances may be caused by foci on the mesial or orbital surface of one frontal lobe. Bitemporal rhythmic disturbances may be caused by a focal epileptogenic lesion deep in one temporal region. The wave and spike pattern of petit mal epilepsy can be reproduced by local stimulation in certain parts of the thalamus.

The EEG may be of assistance in assessing the initial severity and progress of recovery from cerebral trauma due to head injury.

Profound alterations in the EEG occur during the acute stage of any form of encephalitis. Residual changes are of value in prognosis, especially with regard to epileptiform disorders.

In child psychiatry, the EEG may point to an unsuspected organic basis for particularly intractable behavior. However, it is of little value for specific diagnostic purposes except as related to epileptic equivalent states and disorders due to focal lesions or diffuse encephalopathy.

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SPANISH ABSTRACT

Electroencefalografía en la Neurología y Psiquiatría del Niño

Se presenta un relato de los desarrollos principales en la electroencefalografía tal como se ha aplicado en la neurología y psiquiatría del niño durante los últimos 10 años. También se presenta una clasificación de desordenes convulsivos con sus descubrimientos electroencefalográficos característicos.

El EEG es aún el más útil para hacer la diagnosis diferencial entre epilepsia o enfermedades idiopáticas o "genéticas" y trastornos convulsivos que son síntomas de lesiones de cerebro. No obstante hay ciertos descubrimientos electroencefalográficos que siguen las condiciones post-encefalíticas que pueden simular el carácter de las epilepsias idiopáticas, lo que hace que la diagnosis solamente por el EEG es incierta en algunos casos.

La forma de desorden en el EEG en pacientes con trastornos convulsivos no es una guía en la cual se puede depender con relación al tipo o forma del ataque, lo que parece depender principalmente en el área del cerebro donde se origina. Hay una gran variedad de ataques que son causados por el derrame epiléptico focal que surge principalmente en varias áreas de la corteza. Estos pueden ser localizados por el EEG cuando se encuentran en la convexidad de los hemisferios; pero se pueden omitir cuando enterrados en las fisuras o en la superficie ventral o mesial del cerebro. Se descubren frecuentemente solamente cuando los electrodos se colocan directamente en la superficie del cerebro expuesta a la operación.

El derrame epileptiforme de origen subcortical causa trastornos proyectados a ambos hemisferios lo que hace la localización extremadamente dificil por fuera de la cabeza. Aún los foci en la superficie ventral de los lóbulos frontales y temporales pueden activar sistemas rítmicos bilaterales y su verdadera localización se puede encontrar solamente en la operación.

Los electrocorticogramas tomados directamente de cerebro expuesto en la operación han resultado de gran valor al hacer los estudios de localización precisa en pacientes epilepticos de manera que la terapia quirúrgica sea más exacta.

El EEG da información un poco más precisa con respecto a la inteligencia y a la estructura más fina de la personalidad. Sin embargo, en 60 ó 75% de los niños con anormalidades severas de mala conducta se pueden observar en el EEG. Algunos de estos parecen tener una base hereditaria y otros parecen ser debidos a alguna encefalopatía no sospechada. Y otros parecen estar posiblemente relacionados con la maduración retardada del cerebro.

El EEG puede ser de gran ayuda en medir la severidad initial y en seguir el progreso de mejoría del trauma cerebral o de cualquier forma de encefalitis. Las lesiones focales del cerebro debido a tumor, abscesos, trauma o enfermedad vascular local pueden ser exactamente localizados por el EEG en 80 ó 90% de los casos, si se emplea la propia técnica. La diagnosis patológica, sin embargo, puede ser hecha de datos u otros métodos de exámenes clínicos. La hematomata subdural no se diagnostican ni se localizan exactamente con el EEG en aproximadamente la mitad de los casos.

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JET INJECTION IN PEDIATRIC PRACTICE

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JET injection is a new technic of administering substances subcutaneously or intramuscularly without the use of needles or syringes. It represents the first fundamental change in the basic principles of injection in almost 100 years.

The method is based upon the fact that fine jets of adequate pressure are capable of piercing the human skin without producing pain, or causing only slight pain. This is attributable to the fact that the diameter of the jet is only 76 μ, and the cross-sectional area only 1/37 that of a 26 gauge needle, 1/87 that of a 22 gauge needle, and 1/136 that of a 20 gauge needle. Apparently, fewer pain fibers are struck by the jet than by the needle.

The method is of potential importance in the field of pediatrics because it permits injections to be made with a minimum of pain.

METHOD OF INJECTION

Figure 1 shows the injecting instrument, called the Hypospray, and the metal ampoule which contains the drug, called the metapule. Sterile material for injection is placed within the metapule, which is shaped like a blunt-nosed bullet. The anterior tip of the metapule has a hole 0.003 inches in diameter, while the butt end is closed with a rubber plug. The sterile metapule is encased in an aluminum container to avoid contamination before use.

By rotating the metal cuff on the rear of the injecting instrument the plunger is withdrawn into the shaft of the Hypospray and the instrument is cocked for use. By pressing the release button on the rear of the instrument the plunger is driven forward by a calibrated high tension spring mechanism. This is the motive force for the injection.

In order to make an injection, the instrument is cocked, the cap of the aluminum container is removed by the cap remover illustrated in the diagram, and the untouched sterile metapule is dropped from the aluminum case into the anterior end of the instrument. The instrument is now ready for the injection.

The skin of the part to be injected is cleansed with acetone, allowed to dry so that the round nose of the metapule will not slip on the skin, and the skin is placed under slight tension by encircling the part with the hand not holding the instrument. The metapule is pressed firmly and vertically against the skin so that it causes a deep depression of the tissues, and the Hypospray is held snugly in contact with the skin for a period of 2 to 3 sec. after the release button is pressed.

When the release button is pressed, the metal plunger is driven forward against the rubber plug in the butt end of the metapule, so that the material to be injected is forced through the minute opening in the anterior end of the metapule as a jet of extremely fine diameter. The used metapule is then discarded.

The volume of material which can be placed in the metapule for injection is 1.0 cc. By means of a micrometer gauge, any portion of the material in the metapule may be injected, the surplus material being forced from the metapule after it is locked in the cocked instrument and before the injection is made. The work presented in this paper deals with the 0.25 cc. size metapule, which was the only size available until recently.

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The metapule is made of a special alloy which not only has the strength necessary to withstand the high pressure built up within the metapule during the injection, but is practically chemically inert. This latter feature is necessary in order to prevent deterioration of substances kept for long periods of time in the metapule.

Metapules made of the new alloy have undergone testing for a period of 8 mos., the favorable results giving promise that the problem of chemical inertness of the alloy will be solved in the early future. Naturally, the metapules cannot be made available clinically until they satisfy the criteria of the Pure Food and Drugs Administration. Until chemical inertness of the alloy is established the method of jet injection will have only experimental application.

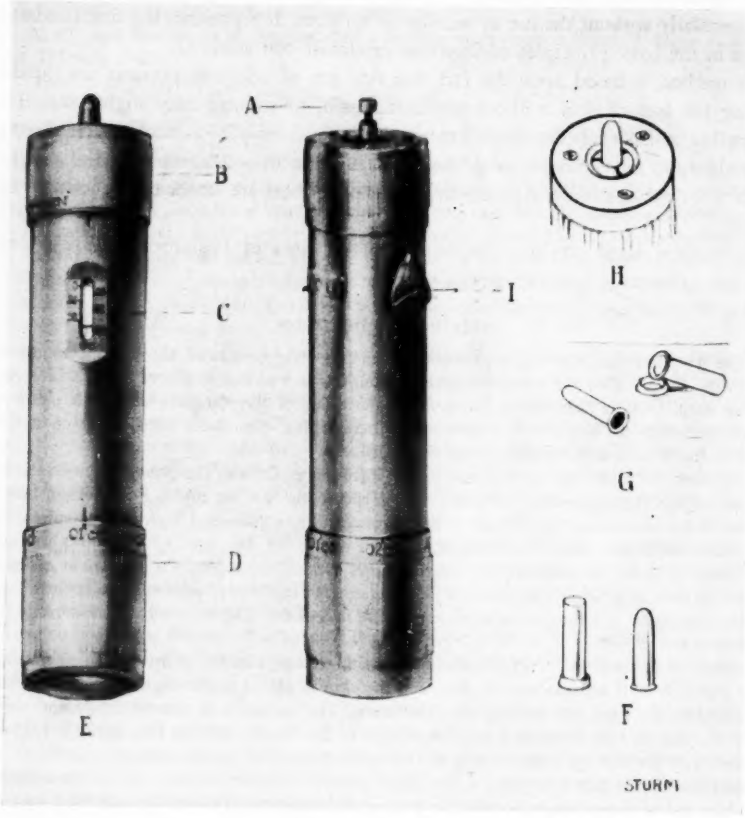

FIG. 1. A. Metallic metapule ejector and plunger.
B. Metapule ratchet lock.
C. Gross micrometer gauge graduated for dispensing solution from 0.05 cc. to 0.25 cc.
D. Fine micrometer gauge for dispensing medication from 0.01 cc. to 0.05 cc.
E. Release button.
F. Capped aluminum container and metapule.
G. Container and metapule with rubber disk in back end.
H. Metapule in ratchet lock.
I. Cap remover of aluminum container G.

Development of the Method

The idea that an instrument could be developed which might inject substances into the tissues with a minimum of pain arose from the observation that fine jets of oil in industrial accidents had been known to penetrate tissues almost painlessly.

The Hypospray instrument has been developed by Robert P. Scherer and James M. McKibbin. The basic anatomic studies were conducted by Figge.[1] Hingson and Hughes[2] have reported previously on clinical studies with jet injection. Hingson and his associates[3] have reported on the treatment of a series of patients having gonorrhea, in whom penicillin was given effectively by jet injection. Hughes, Jordan and Hill[4,10] have reported on the application of jet injection to problems of pediatric practice. Figge has extended his original observations in a more detailed report.[5] Touhy[6] has produced anesthesia at fracture sites by giving jet injections of procaine into the fracture area, permitting painless reduction. Hirsh[7] has investigated blood levels of penicillin and streptomycin given by jet injection. Brown[8] has investigated the possibility of inadvertent intravenous injection with the Hypospray. Hingson and his associates[9] have recently investigated the use of jet injections of procaine to produce nerve block and arrest the pain in leprosy.

Problems Posed by Jet Injection

The development of this new technic of injection poses certain problems which require clarification. Chief among them are: (1) depth of penetration of substances so injected; (2) pain response of individuals given jet injections; (3) local effect on tissues; (4) possibility of inadvertent intravenous injection; (5) maintenance of potency of materials placed in metapules; (6) therapeutic effectiveness of substances given by jet injection; (7) viscosity of material which can be given by this technic.

Depth of Penetration.—The first studies on penetration depth involved the injection of embalmed and unembalmed cadaver material, followed by incisions at the injection sites. In living persons, penetration depth has been studied by the injection of 35% diodrast, followed immediately by the making of roentgenograms,[1,2,4] and by the injection of methylene blue into the tissues at the moment of death, before changes in tissue resistance might be significant.[2] At autopsy, incisions were made to study the depth to which the methylene blue penetrated. Work with children has involved the injection of diodrast, and, to a much less extent, the injection of methylene blue at the moment of death. Tables I, II, and III give the average penetration depth of 310 jet injections of 0.25 cc. of 35% diodrast at 50 pounds spring pressure and at 75 pounds spring pressure in 104 children of

TABLE I

Depth of Penetration of Diodrast Given by Jet Injection in Deltoid Area

Age in Years	50 Pounds Spring Pressure (3 patients for each age)		75 Pounds Spring Pressure (5 patients for each age)	
	Depth (cm.)	Diameter (cm.)	Depth (cm.)	Diameter (cm.)
0–1	1.3	2.1	1.2	2.1
1	1.0	1.1	1.7	2.2
2	0.7	1.3	1.4	1.7
3	0.9	1.2	0.7	1.9
4	1.5	2.1	0.7	2.1
5	0.8	1.6	1.0	2.1
6	0.7	2.0	1.1	1.4
7	0.7	1.1	0.7	1.8
8	0.6	1.2	1.2	2.6
9	0.6	2.1	0.6	1.3
10	0.6	1.8	0.8	1.8
11	0.9	1.1	1.0	2.0
12	0.6	1.0	0.9	1.5

TABLE II

DEPTH OF PENETRATION OF DIODRAST GIVEN BY JET INJECTION IN TRICEPS AREA

Age in Years	50 Pounds Spring Pressure (3 patients for each age)		75 Pounds Spring Pressure (5 patients for each age)	
	Depth (cm.)	Diameter (cm.)	Depth (cm.)	Diameter (cm.)
0–1	1.1	1.3	1.1	1.8
1	1.2	1.2	1.5	1.9
2	0.7	1.1	1.1	1.4
3	1.0	1.4	0.9	1.8
4	1.2	1.8	0.8	1.9
5	0.7	1.9	0.7	2.1
6	0.7	1.4	1.0	2.1
7	0.8	1.5	1.1	2.1
8	0.5	1.6	1.0	2.8
9	0.9	1.9	0.8	1.9
10	0.7	2.2	0.9	2.7
11	0.7	1.9	0.9	2.2
12	0.7	1.6	0.8	1.6

various ages. Injection sites were the deltoid, triceps, and lateral thigh areas. Observations for diodrast sensitivity manifestations were made between injections in the same child, but none occurred.

The purpose of these studies was to determine spring pressures of the instrument necessary to permit either subcutaneous or intramuscular injections to be made in children of various ages.

Observations on penetration depth may be summarized, both in this study and in other work now in progress, by stating that a spring pressure of 75 pounds is the desirable strength for instruments to be used for children under 10 years of age, and that 100 pounds spring pressure is the desirable strength for instruments to be used in children 10 years of age or older. Instruments of 50 pounds spring pressure are not adequate.

With instruments of these spring pressures it has consistently been possible to secure subcutaneous injections when the Hypospray is fired over the lateral thigh area, and intramuscular injections when

TABLE III

DEPTH OF PENETRATION OF DIODRAST GIVEN BY INJECTION IN LATERAL THIGH AREA

Age in Years	50 Pounds Spring Pressure (3 patients for each age)		75 Pounds Spring Pressure (5 patients for each age)	
	Depth (cm.)	Diameter (cm.)	Depth (cm.)	Diameter (cm.)
0–1	1.5	1.5	1.1	2.5
1	0.9	1.1	1.5	2.3
2	0.8	1.2	1.1	2.3
3	0.8	1.6	0.9	1.9
4	0.6	1.4	0.9	2.3
5	0.7	2.0	0.8	2.1
6	0.65	1.9	0.7	1.9
7	0.5	2.0	0.7	1.8
8	0.6	1.9	0.6	1.6
9	0.8	1.6	0.9	2.1
10	0.6	2.3	1.0	1.9
11	0.36	1.2	0.6	2.3
12	0.5	1.16	0.9	1.9

the instrument is fired over the deltoid or triceps areas. The fact that the fascia lata stops the force of the jet assures subcutaneous injections when the lateral thigh area is used.

Pain Response.—The chief advantage of jet injections is that they are relatively painless. Detailed evaluation of pain response in 321 children given over 1,000 jet injections has shown that the great majority of them gave no evidence of having experienced pain.

In studying pain response the following factors were observed: (1) the age of the child, (2) whether the child was crying before the injection was actually given, (3) whether the child jumped at the click the present model of the Hypospray makes when it is fired, and (4) whether the substances injected seemed to produce a stinging sensation, as indicated by the statements of older children.

The greatest difficulty in evaluating pain response has been in the work with small children, especially apprehensive infants in hospital wards where painful procedures have already been carried out on the infants and where separation from parents has disturbed the children.

There appear to be three things which govern the pain response of individuals given jet injections: (1) the force of the jet itself, (2) the nature of the substances injected, and (3) the individual's threshold for pain. While the force of the jet itself is constant, the other two factors vary. For example, there was a higher frequency of pain in the use of purogenated diphtheria-tetanus toxoid, although the fact that infants were being injected made it somewhat difficult to evaluate pain response. That the individual's threshold for pain partly governed the response was shown by the fact that many older children given repeated injections showed no evidence of pain, while other older children did show pain with each injection of the same substance. For instance, one 9 year old boy received 80 jet injections of penicillin at 3 hour intervals and stated that he felt no pain with any of the injections.

In order to study pain response under the most carefully controlled conditions, a group of 62 children over 2 years of age were given 0.25 cc. of normal saline with a Hypospray of 75 pounds spring pressure. Of these, 58 did not cry when the injection was made, while 4 did cry. Of the 54 children who made a definite statement with regard to what they felt when the injection was made, 49 stated that it did not hurt at all, while 5 stated that it "stung" or "pinched."

When 104 patients were given 310 jet injections of 0.25 cc. of 35% diodrast the findings were as follows. Of the 310 injections, in 69 instances the children were crying before and at the time the instrument was pressed against them, leaving 241 instances in which pain response to diodrast could be evaluated. Of the 241 injections 239 did not cause the children to cry, while crying did occur in 2 instances. Of the 195 instances in which definite statements concerning pain response were made, there were 157 statements that no pain was felt, and 38 statements that the injection "stung" or "pinched."

Twenty-five children over 2 years of age, who were not crying before the injection, or when the instrument was pressed against them, were given jet injections of 0.25 cc. of penicillin 25,000 units in normal saline with a Hypospray of 75 pounds spring pressure. Of these, 24 did not cry when the injection was made, while 1 did cry. Of the 24 statements made after the injection, 17 stated that the injections did not hurt, while 7 stated that the procedure "stung" or "pinched."

There was a higher frequency of pain associated with jet injections of purogenated diphtheria-tetanus toxoid, but, since the substance itself may have been more irritating, further comments on this phase of pain response will be reported later, when a greater series of patients has been studied and different types of toxoids have been used.

Pain response studies of children treated with jet injections of penicillin for various diseases have not been evaluated statistically, since many of the injections were given by nurses who had just learned to use the instrument, a large proportion of the children were infants, and the injections were given on busy wards where upset children were disturbing other children. Still, there was a marked decrease in evidence of pain when the Hypospray was substituted for the needle and syringe. Older children began asking for the "flashlight" which gave the injections without pain.

Local Effect on Tissues.—In over 1000 jet injections there has been practically no visible damage to tissue, with the following exceptions. In the early stages of acquiring proficiency with the instrument a few slight cuts and bruises are likely to be produced; these can largely be prevented as familiarity with the use of the Hypospray is achieved. The technic of the injection is simple to learn. These slight cuts and bruises are, for the most part, due to the rounded tip of the metapule slipping on the skin when the skin is not allowed to dry completely after cleansing with acetone and when

the instrument is not held firmly and vertically against the tissues for a period of 2 to 3 sec. after the release button is pressed. Even if a slight cut is produced it is superficial.

After one is familiar with the technic of the injection slight bruises may still occur if the child happens to jerk at the time the injection is given, or if a small superficial vessel happens to be struck by the jet. The rarity of these bruises which occur after one is familiar with the instrument is shown by the fact that they occurred less than 10 times in 1000 consecutive injections.

Careful observations of patients given repeated jet injections of various substances have failed to reveal any nodules in the underlying tissue, or any evidence of local atrophy. However, in 4 out of 131 injections of purogenated diphtheria-tetanus toxoid given to Negro infants minute keloid formation at the site of injection occurred. These tiny keloids were from 1 to 2 mm. in diameter and were slightly linear. Such keloid formation was not seen in Negro patients given other substances by jet injection, and the possibility remains that a small amount of the toxoid may have remained in the skin and may have stimulated the keloid formation.

In 12 biopsies made at intervals of 24, 48, and 72 hours after jet injections of 0.25 cc. of physiologic saline the tissues were completely normal in 10 instances, and showed mild hemorrhagic extravasation in the subcutaneous tissues in 2 instances. Both of these latter biopsies were from the same patient, an elderly debilitated man with carcinoma.

The probable reasons why jet injections are practically innocuous to tissues are that the cross-sectional area of the jet is much smaller than the cross-sectional area of needles commonly used for injections, and that the force of the jet has been calculated to be only 11 gm. This is stated[5] to be less than the force required to thrust needles of the usual sizes through human skin.

Possibility of Inadvertent Intravenous Injection.—When injections are made by needle and syringe technic it is possible to withdraw the plunger to determine whether the point of the needle is in a vein. Obviously, this is impossible with jet injections. For this reason, the possibility arises that materials given by jet injection might inadvertently enter a vein.

Figge[5] gives reasons for thinking this would be unlikely. The firm pressure of the instrument against the skin probably flattens superficial vessels, the jet is of extremely fine diameter, and the injecting force has been calculated[5] to be about 11 gm. Brown[6] exposed the jugular veins of dogs and made jet injections directly over the veins. When epinephrine was given in this manner significantly large amounts entered the jugular vein in some of the experiments. He cautions against making jet injections in the neighborhood of large vessels unless the substance used is pharmacologically safe for intravenous administration. This is a reasonable precaution which holds true also for injections with needle technic.

In approximately 200 consecutive jet injections of purogenated diphtheria-tetanus toxoid into infants there have been no reactions, and no evidence suggestive of significant intravenous injection.[10] Since immunization by jet injection is being extended to a larger group of patients in this clinic, it should be possible as time goes on to determine whether there is any real hazard involved. Triple vaccine containing diphtheria, tetanus and pertussis agents will receive clinical trial. A military immunization program using jet injection on a large scale is starting, and will afford additional opportunities to evaluate the hazard of intravenous injection. The danger is probably more theoretical than practical. Considering how often infants wriggle and twist during needle injection of vaccines it would be remarkable if an occasional patient did not receive his vaccine intravenously by this technic.

Probably the simplest way to find the answer to the problem would be to study the absorption speeds of radioactive isotopes given by jet injection, as compared to absorption speeds of the same agents given into veins.

Even if it were shown that in the occasional patient some of the material entered a vein it would not prevent use of the method for injection of a wide variety of substances which carry no danger if given intravenously.

Maintenance of Potency of Materials Placed in Metapules.—One of the difficulties in the development of the technic of jet injection has been the production of a metal alloy which would be chemically inert, or sufficiently so to permit substances contained in the metapules to retain their potency for long periods of time. It is apparent that the method is based upon the fact that drugs for injection would be dispensed already loaded under sterile conditions in the metapules and that the metapules would have to have a sufficiently long shelf life.

The work which has been reported in this paper was done with metapules made of nickel, which does not satisfy the need for chemical inertness. Therapeutic substances given by jet injection in this work have been loaded into the metapules under sterile conditions on the day of injection.

It has already been mentioned that an alloy with sufficient strength to withstand the pressure built up within the metapule and with promising evidence of chemical inertness has been developed. It appears likely that the problem of the metapule will be solved shortly. The instrument cannot be made available until this problem is solved.

Effectiveness of Substances Given by Jet Injection.—Studies of Hingson and his associates[3] have shown that acute gonorrhea responds as well to penicillin given by jet injection as it does to penicillin given by needle technic. In a previous communication[4] it was found that, in a small series of patients, penicillin blood levels were as high following jet injection as when the same amounts of penicillin were given by needle. Hirsh[7] has reported good levels of penicillin and of streptomycin following jet injection of these agents.

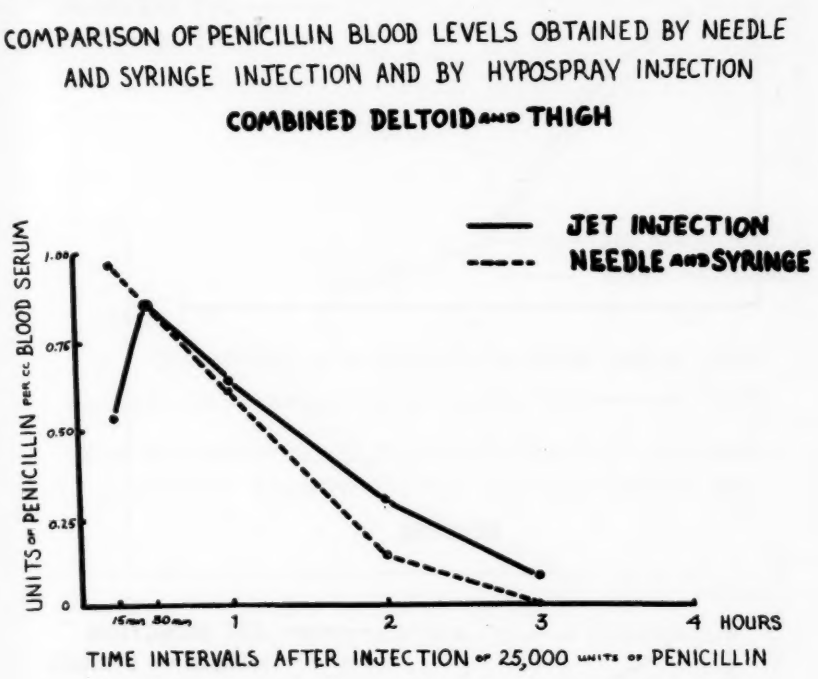

FIG. 2. Penicillin blood levels with Hypospray contrasted with those with needle and syringe.

Penicillin Blood Levels. Forty children of various sizes were given single injections of 25,000 u. of penicillin in 0.25 cc. of normal saline. These children had had no previous penicillin, streptomycin or sulfonamide therapy. One half of the children were given penicillin by jet injection, and one half were given the agent by needle and syringe technic. Two sites of injection were included in the studies: (1) the deltoid area, and (2) the lateral thigh area. Half of the children received their injections in the deltoid area and half in the lateral thigh area. Venous blood was drawn at intervals of 15 min., 30 min., 1 hr., 2 hrs., 3 hrs., and in some cases 4 hrs. after the injections. The method used for the determination of penicillin levels in the specimens was the inhibitory effect of B. subtilis in serial dilutions of serum (see Figure 2).

It will be noted that demonstrable levels of penicillin are maintained for 3 hours following jet injections of 25,000 u. in normal saline. Furthermore, the blood levels in patients given penicillin by jet injection are higher, at the end of the 1st hour, than the levels of patients receiving the same amount of penicillin by needle technic, and the levels in the "jet" patients remain appreciably higher for the period of 3 hours than those of the "needle" patients.

Twenty children with various types of infections for which penicillin was considered indicated

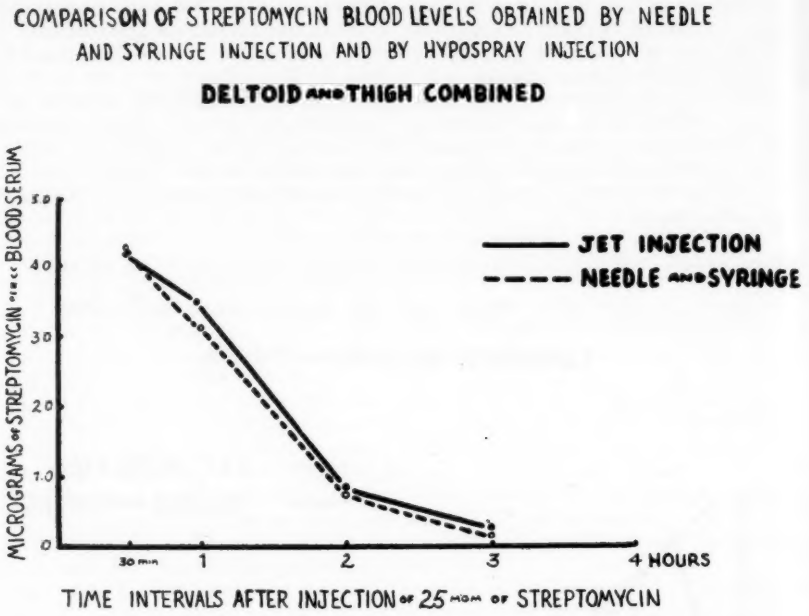

FIG. 3A. Streptomycin blood levels with Hypospray contrasted with needle and syringe.

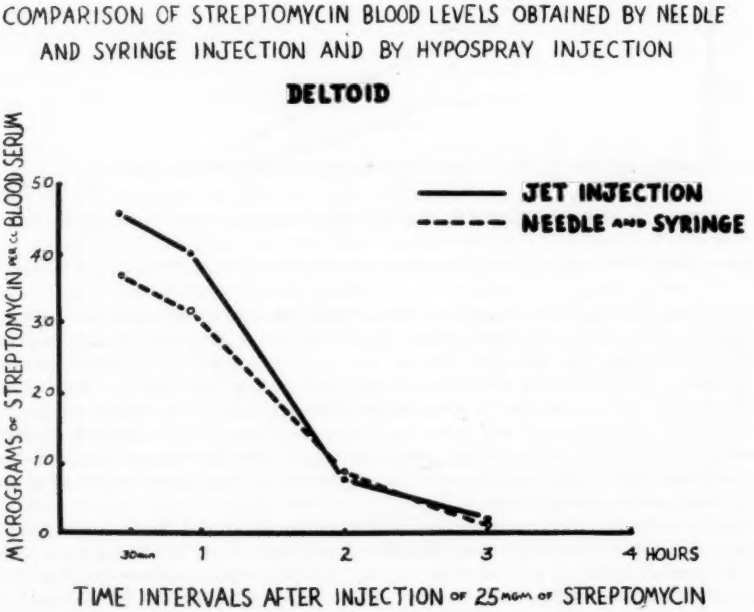

FIG. 3B. Streptomycin blood levels contrasted after injection in deltoid area.

were given jet injections of 25,000 u. of penicillin in normal saline every 3 hours. In 10 of the patients it was determined that a penicillin-susceptible organism was the cause of the infection. In the remaining 10 patients cultures were not obtained, but the clinical evidence indicating the need for penicillin therapy was clearcut.

The 20 patients responded quickly to the jet injections and made rapid recoveries. There was no noticeable difference in the way they responded, as compared to patients with similar infections given the same quantity of penicillin by needle technic.

Streptomycin Blood Levels.—The method used for this study was similar to that for studying penicillin blood levels. A single injection of 25 mg. of streptomycin base in 0.25 cc. of saline was given to 40 patients. The method used for streptomycin level determinations was the inhibitory effect on B. circulans in serial dilutions of serum. Figures 3A, 3B, and 3C show the results obtained.

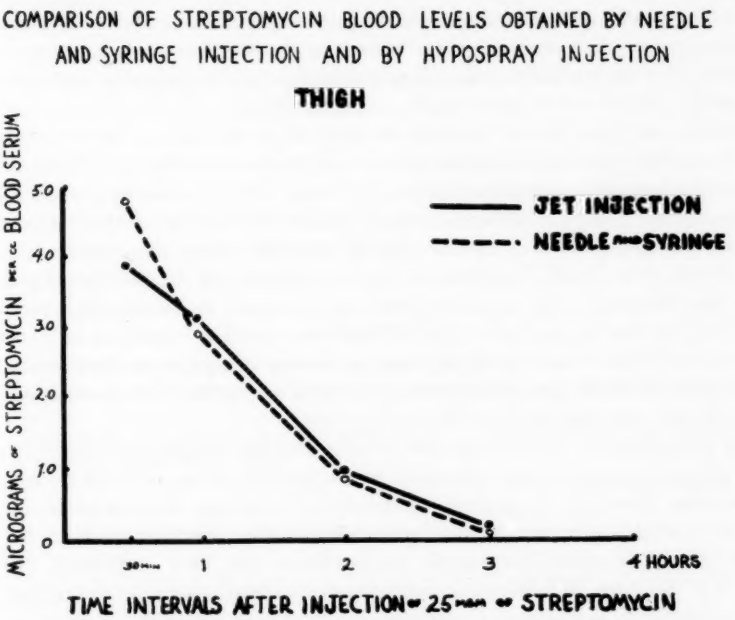

FIG. 3C. Streptomycin blood levels contrasted after injection in lateral thigh area.

It will be seen that demonstrable levels of streptomycin are maintained for 3 hours after jet injections of 25 mg. of streptomycin in saline.

Previously, Hingson and Hughes[8] had reported the painless control of a diabetic child for a trial period of 2 weeks during which protamine insulin was given by jet injection. Studies on the application of jet injection to the treatment of diabetic patients are being extended.

Hingson[8] has used jet injections of procaine to anesthetize tissues prior to the introduction of spinal puncture or caudal analgesia needles. Touhy[6] has produced anesthesia at fracture sites by jet injections of procaine into the fracture area, permitting painless reduction. Hingson[9] has produced peripheral nerve block in cases of leprosy having extreme radiating pain, and the method is now receiving widespread application at the leprosarium at Carville, La. Brody has effectively anesthetized the "trigger points" of a large series of patients with fibrositis and similar painful lesions.[10]

Viscosity of Substances Which Can Be Given.—One of the problems of the technic is the viscosity of substances which can be fired through the minute orifice of the metapule. The two problems involved are the initial viscosity of the material placed in the metapule, and the settling or precipitating effect which heavy suspensions might undergo if left in metapules for long periods of time. Most of the work done so far has dealt with saline or aqueous solutions of substances which have been

loaded in the metapules shortly before the injections were made. No conclusive studies have been made on more viscous substances left for long periods in metapules. Investigations of this type were deliberately deferred during the time the new alloy was being developed, because it was recognized that nickel, the metal used in the metapules until recently, would not be the metal used in the future. It is apparent that studies of this sort must be conducted before certain viscous substances can be employed by jet injection.

Discussion

The chief advantages of jet injection are its painlessness and the simplicity of the technic, which does not involve sterilizers, needles, syringes, and cleansing of equipment. Clinical application of the technic is less time-consuming than sterilizing equipment, assembling needle and syringe, withdrawing medication from a container, giving the injection, and washing the equipment. Nurses on the pediatric wards have expressed a preference for jet injections because they require less time and trouble and, especially, because the children submit more readily to the injections.

Provided the possibility of intravenous injection is excluded by further study and experience, the technic would appear to be of real promise in the field of immunizations, especially in pediatrics where the relative painlessness would be most appreciated. While certain selected groups of children, such as diabetic and allergic children who receive repeated injections, can be trained to take the injections calmly, the majority of infants and children given needle injections do resist the needle, and are difficult to handle for some time thereafter. One important advantage in regard to immunization procedures would be that viral agents, such as that of infectious hepatitis,[11] could not be transmitted from one individual to another by improper sterilization of equipment. Such an advantage would apply chiefly to mass immunization procedures where there is increased opportunity for ineffective sterilization of needles and syringes.

The development of long-acting types of penicillin, by reducing the number of injections given, has gone a long way to eliminate the pain of repeated needle injections of penicillin. However, if the single remaining daily injection could be made relatively painless it would be an advantage. A type of long-acting penicillin which can be given by jet injection is under investigation, but insufficient data have accumulated to report upon it at this time. In fulminating infections due to penicillin-sensitive organisms, it is still preferable to give repeated injections of pencillin in saline, or constant penicillin drips.

The application of jet injections of insulin has not been adequately explored, but the possible advantages of a relatively painless method of injection are obvious.

No studies on hormone substances have been made, other than the injection of epinephrine and insulin. The field of jet injection of hormone agents, especially for those individuals committed to long courses of injections, deserves further study.

A number of drugs widely used in hospital practice, such as morphine, atropine, and sedative agents, have not, as far as is known, been given by jet injection.

The use of jet injection of procaine for anesthetizing relatively small areas, or to produce peripheral nerve block, has been mentioned.

Summary and Conclusions

The technic of jet injection is described. It represents the first fundamental change in the basic principles of injection in almost 100 years.

The method is relatively painless, is practically innocuous to tissue, and has technical simplicity.

Information is presented dealing with depth of penetration of substances injected, pain response of children, local effects on tissues, blood levels of penicillin and of streptomycin given by jet injection, and clinical response of patients given penicillin by this technic.

Discussions are given concerning the need for chemical inertness of the metal used in the metapule, viscosity of material which can be injected and the possibility of inadvertent intravenous injection.

The proper instrument for children under 10 years of age is one of 75 pounds spring pressure, and for children 10 years of age or older 100 pounds spring pressure. With these strengths it has consistently been possible to secure intramuscular injections in the deltoid and triceps areas, and subcutaneous injections in the lateral thigh area. Injections over large veins should obviously be avoided.

Jet injection offers promise in the field of pediatrics chiefly because of its relative painlessness. It may prove of value in mass immunizations, not only because of pain prevention and technical simplicity, but also because the transmission of viral agents from one subject to another by contaminated needles would be avoided.

Further investigations are indicated, for the relief of pain is one of the foremost functions of a physician.

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Spanish Abstract

Inyección "Jet" en la Práctica Pediátrica

Se describe la técnica de la inyección "Jet." El método es relativamente sin dolor, casi innocuo al tejido, y de simplicidad técnica.

La información se presenta con relación a la profundidad de penetración de sustancias inyectadas, el resultado doloroso de los niños, los efectos locales en los tejidos, cantidades de sangre de penicilina y de estreptomicina que se ponen mediante la inyección "jet," y la respuesta clínica de los pacientes dada a la penicilina por medio de esta técnica.

Se presentan tratados con relación a la necesidad de inercia química del metal usado en la metapula,

viscosidad de la materia que puede ser inyectada, y la posibilidad de inyección intravenosa inadvertente.

El propio instrumento para niños de menos de 10 años de edad parece ser uno de 75 libras, presión de resorte, y 100 libras de presión de resorte para niños mayores de 10. Con estas fuerzas ha sido posible consecuentemente poner inyecciones intramusculares en las áreas deltoides y tríceps, y subcutaneas en el área lateral de la cadera. Hay que evitar inyecciones en las venas grandes.

La inyección "Jet" es una promesa en el campo de la pediatría, principalmente a causa del poco dolor que causa. Puede dar resultado y ser de valor en las inmunizaciones en masa, no solamente porque no causa dolor y su simplicidad técnica sino que también porque la transmisión de agentes infecciosos de un sujeto a otro mediante agujas contaminadas se evitará.

20 South Dunlap St.

CONGENITAL HEMOLYTIC DISEASE RESULTING FROM A-O ISOIMMUNIZATION

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Brooklyn, N.Y.

THE relationship of maternal and fetal Rh incompatibility to congenital hemolytic disease is well established. With the increase in the number of cases of hemolytic disease which have come under investigation, there has developed an awareness that occasionally this disease of the newborn may occur in infants born to Rh positive mothers. Investigation of the mothers' serum in these cases has failed to reveal demonstrable Rh or Hr antibodies. As a result of this fact, the possible role of the major agglutinogens A and B in the etiology of hemolytic disease of the newborn has received increasing attention.

Potter,[1] in her monograph on the Rh factor, has questioned the acceptance of this mechanism of A and B isoimmunization. The opposite point of view is held by Polayes[2,3] who reported a group of nine cases of hemolytic disease attributed to isoimmunization of group O mothers by group A infants. In his most recent publication on this subject Polayes[4] has demonstrated in a series of 350 cases that the anti A and anti B agglutinin titers were most significantly elevated in multiparas with heterospecific blood group pregnancies as compared to those women with compatible blood group pregnancies, nulligravida and children. Furthermore, the anti A or B agglutinin titers were highest in those heterospecific pregnancies which terminated in a clinical picture in the infant indistinguishable from congenital hemolytic disease.

Other investigators have noted similar significant findings in heterospecific blood group pregnancies. Halbrecht[5] studied three groups of infants. In the first group, the so-called "icterus precox," 95% of 60 infants studied showed blood groups incompatible with those of the mothers, while of 160 infants with "physiologic" jaundice only 30% of the infants showed incompatible blood group findings, and 26.5% of 2,000 normal infants showed similar incompatibility. A study of 15 infants with icterus precox showed that all 15 mothers belonged to group O, while 12 infants belonged to group A and three infants belonged to group B. Boorman, Dodd and Mollison[6] showed that in 25 of 29 heterospecific A-O pregnancies, an increase in anti A titer was demonstrated, while 11 of 15 B-O cases showed a similar rise in anti B titer, reaching a maximum between the 10th and 20th day following delivery. None of 13 compatible pregnancies showed any significant rise in either anti A or anti B titers.

The relative infrequency of cases of hemolytic disease of the newborn caused by major blood group incompatibilities as discussed above has been explained by Tovey[7] by the relative lack of permeability of A and B agglutinins through the placental barrier,

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as well as by neutralization of the anti A and anti B agglutinins by group specific substances present in the fetal plasma. The importance of the tissue cell content of A and B agglutinogens in the prevention of untoward hemolytic mechanisms in this group of cases has been stressed, since it has been estimated that only 20% of infants are "nonsecretors."[5] However, Wiener[8] has demonstrated that even secretors can develop A-O or B-O isoimmune hemolytic episodes. That most cases of A-O incompatibility result in relatively minor hemolytic episodes should not serve as an argument against the acceptance of this mechanism in causing congenital hemolytic disease. In Polayes[9] series of nine cases, two instances of fatal disease were recorded, with one case showing kernicterus. In Wiener's series of 42 cases, two fatalities were described, but in one case the autopsy findings were inconclusive, and in the other there was a complicating Rh isoimmunization. Becker and Vogel[10] attribute one of their seven cases of kernicterus to A-O isoimmunization but no serologic details are included. It is the purpose of this presentation to record in detail three additional fatal cases of hemolytic disease of the newborn in all of which kernicterus was present and all of which are believed to be the result of A-O isoimmunization.

Report of Cases

Case 1. An apparently normal female infant was delivered spontaneously after an uneventful full term pregnancy. The mother was a 33 yr. old para II, gravida III. She was Rh positive, group O and had a negative Wassermann reaction. There were 2 living children, then 7½ and 3 yrs. of age, who had never had jaundice and were in good health. The mother had never received any blood transfusions.

Physical examination of the baby revealed no abnormalities. Skin was clear, and she weighed 2.65 kg. During the 24 hours following delivery she gradually developed marked icterus. Blood count revealed RBC 3.4 million/cmm. and Hgb. 13.6 gm./100 cc. There were 50 nucleated red blood cells per 100 white cells. A transfusion of group A, Rh negative blood 50 cc. was given.

She was still markedly jaundiced on the 2nd day; feedings were taken poorly but the cry was strong. RBC count at this time was 4.0 million/cmm. with Hgb. 15 gm. There were 100 nucleated red blood cells per 100 white cells. A second transfusion of group O, Rh negative blood 55 cc. was administered.

Jaundice was still marked on the 4th hospital day, and the cry was weak. Response to stimulation was sluggish. RBC count was 4.25 million/cmm. with Hgb. 12.1 gm./100 cc., and 35 nucleated red blood cells per 100 white cells were seen on the smear. Her condition rapidly deteriorated and she appeared critically ill. Sucking reflex disappeared. Liver edge was palpable; spleen was not felt. Temperature rose to 39.5° C. and the infant died 72 hrs. after birth. Complete blood studies of the mother, father, siblings and baby showed the following:

	Blood Group	Rh type	Hr′
Father	A	Rh_o	positive
Mother	O	Rh_1 Rh_2	positive
7½ yr. old sibling	O	Rh_o	positive
3 yr. old sibling	O	Rh_o	positive
Baby	A	Rh_o	not done

Examination of the mother's blood taken 12 days following delivery revealed an anti A agglutinin titer of 1:10,120 and anti B titer of 1:320. Reexamination of the mother's blood 2 weeks later showed a decline in the anti A titer to 1:1280, while the anti B titer was 1:640. Dilutions of the mother's serum in albumin-plasma mixture yielded an anti A titer of 1:320. No Rh or Hr antibodies were demonstrated.

Autopsy findings: Body is that of a deeply jaundiced female infant. A few cubic centimeters of yellow fluid are present in the peritoneal cavity. Wt. 2610 gm.; ht. 41 cm. from crown to heel. Spleen is not greatly enlarged, weighing 10 gm. Liver is considerably enlarged weighing 200 gm. and extends inferiorly almost to the level of the iliac crest. Brain weighs 340 gm. An intense yellowish pigmentation is found in the dentate nuclei of the cerebellum, in the medullary olives, the hippocampal gyri and the basal ganglia, particularly in the thalami. Microscopically the lungs show

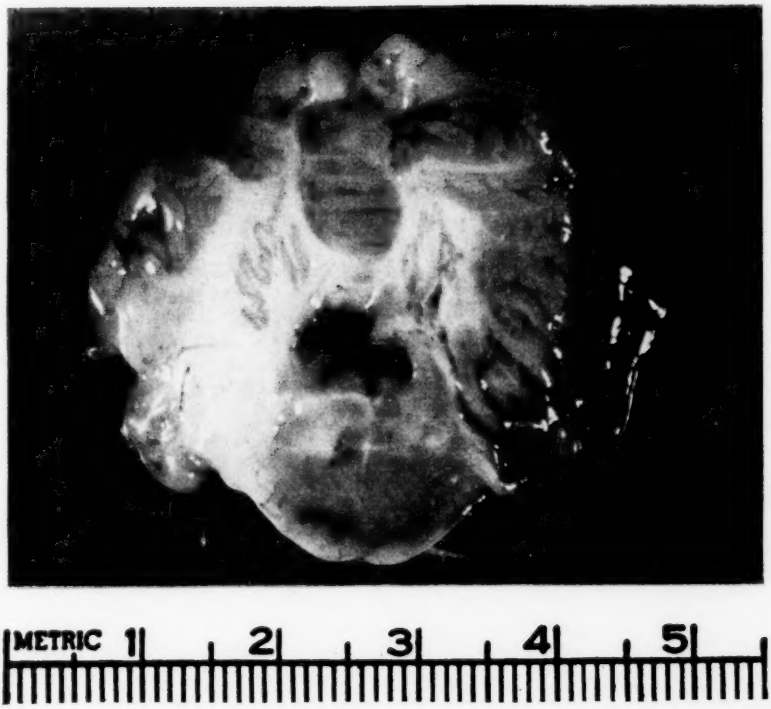

FIG. 1. Sagittal section through brain stem and cerebellum showing intense yellow pigmentation of cerebellar dentate nuclei and of periventricular pontine nuclei.

aspirated bile-stained amniotic contents with abundant acute reactive inflammatory change. There is diminished prominence of the splenic Malpighian follicles with marked congestion of the red pulp and prominent erythropoietic foci both in the pulp and in the larger arteries. Numerous hematopoietic foci in the sinusoids, bile staining of the hepatic cells and presence of bile casts in the canaliculi are noted in the liver. Bone marrow exhibits moderate hyperplasia of both myeloid and erythroid tissue. Necrobiotic changes in the nerve cells, particularly in the medullary olives, are apparent in the brain. Final anatomic diagnoses: congenital hemolytic disease with hepatomegaly; kernicterus involving cerebellar nuclei, medullary olives, basal ganglia and hippocampal gyri; aspiration of amniotic contents with bronchopneumonia.

Case 2. A 37 yr. old para I, gravida II, was delivered by low forceps of an apparently normal full term female infant. Mother was Rh positive, group O and had a negative Wassermann reaction. General appearance, nutrition and color of the baby were good after delivery. Birth wt. was 3.6 kg. She developed deep jaundice within 24 hours, although general appearance was good and liver and spleen were not palpable. RBC count was 3.6 million/cmm. with Hgb. 15.1 gm./100 cc. There were 4 nucleated red blood cells per 100 white cells. Seventy-five cc. of group O, Rh negative blood were given by transfusion. Following this, she appeared more alert. Hemoglobin on the same evening was 15.2 gm. and a smear showed 60 nucleated red blood cells per 100 white cells.

Jaundice was still marked on the following day but liver and spleen were not palpable. Urine was dark in color; the temperature was normal. There were 5.0 million/cmm. red blood cells with Hgb. 16.5 gm./100 cc., 60 thousand white blood cells with polymorphonuclears 80% and 25 nucleated red blood cells per 100 white cells.

Temperature rose to 39.2° C. on the 4th hospital day. Infant was markedly jaundiced and listless. RBC count was 5.2 million/cmm. with Hgb. 16.5 gm./100 cc. No nucleated red cells were seen. On the 5th hospital day, respirations became labored, the cry was weak and the sucking reflex was poor. Small pustular lesions appeared in the skin of the right axilla. Blood count at this time revealed RBC 4.5 million/cmm., Hgb. 15.0 gm./100 cc., WBC 22.0 thousand/cmm. with no nucleated red cells seen. Spasmodic movement of the head and twitchings of the eyelids became apparent. The baby vomited blood-streaked mucoid material and died quickly, 114 hours after birth.

Blood studies carried out on the members of this family showed the following:

	Blood Group	MN Type	Rh Type	Hr′
Father	A	M	negative	positive
Mother	O	M	Rh_2	positive
3 yr. old sibling	A	M	Rh_2	positive
Baby	A	M	Rh_2	positive

Examination of the mother's serum 8 days after delivery revealed an anti A agglutinin titer of 1:5000. Serum diluted in albumin-plasma mixture agglutinated A cells in a titer of 1:1000. Three weeks later, the anti A titer had fallen to 1:1280. Seven months later, the anti A titer was 1:320. No Rh or Hr antibodies were demonstrated in the mother's serum. Examination of the infant's serum failed to reveal any evidence of agglutinating substances.

The sibling 3 yrs. of age was also delivered at term, and became jaundiced shortly after birth. Blood count 6 days after delivery showed RBC 2.3 million/cmm. with Hgb. 11.4 gm./100 cc. After a single transfusion of group A, Rh negative blood 55 cc. the red cell count rose to 3.4 million/cmm. with Hgb. 13.2 gm./100 cc. and there were 10 nucleated red cells per 100 white cells. The hemoglobin and red blood cell count rose rapidly thereafter and the child made an apparently uneventful recovery. She sat up at 5 months of age and walked at 16½ months but at the age of 2 the parents noted that she was almost completely deaf. Mental development has apparently not progressed normally.

Autopsy findings: Body is that of a white female infant weighing 3,630 gm. and measuring 49 cm. from crown to heel. Deep jaundice is present throughout the skin. Small pustules are present in the region of the left clavicle and axilla and in the left inguinal region. Spleen is enlarged to twice its normal size and weighs 20 gm. It is dark red in color and soft in consistency. Liver is slightly enlarged, weighing 165 gm. No abnormalities are seen on section. Brain is moderately enlarged weighing 420 gm. After fixation marked yellow pigmentation of the medullary olives, the dentate nuclei of the cerebellum and of the periventricular nuclei of the pons is noted (Fig. 1). Similar yellow discoloration is seen in the hippocampal gyri, the caudal portions of the caudate nuclei, the mammillary bodies and the medial portions of the thalami. Microscopically bile-stained amniotic

fluid is found in the pulmonary alveoli. The follicles appear small and there is a prominent eosinophilic leucocytic infiltration of the follicles in the spleen. The red pulp is congested but no excessive hematopoiesis is found. Section through the umbilical vein reveals limited acute inflammatory infiltration of the intima. Small foci of hematopoiesis are present in the hepatic sinusoids. Occasional large multinucleated giant cells containing lobulated basophilic nuclei and irregular eosinophilic cytoplasm and resembling megakaryocytic cells are found. The portal triads are prominent and practically all are infiltrated by numerous adult eosinophilic leucocytes and by immature hemopoietic cells. Many of the nerve cells in the brain especially in the periventricular pontine nuclei show a rounding of the cytoplasmic borders, pyknosis of the nuclei and a yellow-brown staining of the cytoplasm. The neuroglial ground substance in this focus also shows similar yellow staining. No intravascular capillary thrombi are found in many sections studied. Sections of the bone marrow reveal moderate hyperplasia of the myeloid and erythroid series with a moderate increase in eosinophilic myelocytes. Final anatomic diagnoses: congenital hemolytic disease with hepatosplenomegaly: kernicterus involving medullary olives, cerebellar dentate nuclei, periventricular pontine nuclei, hippocampal gyri and caudate and thalamic nuclei; aspirated bile-stained amniotic contents with reactive bronchopneumonia; eosinophilia of splenic follicles, liver and bone marrow.

Case 3. A premature male infant of approximately 34 weeks' gestation was delivered spontaneously after an uneventful labor. Except for moderate cyanosis at birth no abnormalities were noted. He was placed in an incubator and received continuous oxygen by funnel and Vitamin K 2.4 mg. every 6 hours for 6 doses. Slight jaundice became evident on the 3rd hospital day. Liver and spleen were not felt. Blood count showed Hgb. 18.5 gm./100 cc., RBC count 5.4 million/cmm. and WBC count 7.0 thousand with neutrophiles 29%, lymphocytes 68% and eosinophiles 3%. Progressively increasing jaundice was noted on the 5th hospital day. Icteric index at this time was 20. The cry was weak and rolling of the eyes was noted. Episodes of cyanosis became more frequent. Blood count at 1 wk. of age showed a Hgb. 10.8 gm./100 cc. with RBC 3.6 million/cmm. No erythroblasts were noted in the peripheral smear. His blood was in group A and was Rh positive. Thirty cubic centimeters of group O, low agglutinin-titered blood to which Witebsky substance had been added was administered by transfusion. He became progressively worse and died on the 6th hospital day. Complete blood studies performed on the mother, father and infant showed the following:

	Blood Group	Rh type	Hr′
Father	A	Rh_1	positive
Mother	O	Rh_1	positive
Baby	A	Rh_1	negative

An investigation of the mother's serum in saline dilutions collected 12 days postpartum revealed an anti A titer of 2,048 and an anti B titer of 128. Similar titers done on serum diluted with an albumin-plasma mixture revealed an anti A titer of 6,000 and an anti B titer of 256. When 1 part of the mother's serum was mixed with 2 parts of A and B blood group specific (Witebsky) substance and the resultant mixture was diluted with saline, titration with group A cells showed complete failure of agglutination. Corresponding dilutions of the serum adsorbed by A and B blood group specific (Witebsky) substance performed in albumin-plasma mixture yielded a titer of 512. When these determinations were repeated on the mother's serum 16 days later the results were as follows: anti A in saline 2,048, anti B in saline 4; anti A in albumin-plasma 1,024. Serum adsorbed with A and B blood group specific (Witebsky) substance at this time failed to agglutinate group A cells in saline and showed a titer of 4 when dilutions were made in albumin-plasma.

Postmortem blood obtained from the baby was investigated with regard to the anti A agglutinin content. Dilutions of the baby's serum in saline failed to agglutinate group A cells from the father and from another group A donor. When these serum dilutions were made with albumin-plasma mixture a titer of 9,000 was obtained. After addition of the baby's serum to A and B blood group specific (Witebsky) substance this titer fell to 4,096. No atypical Rh or Hr antibodies were found in the maternal serum.

At the suggestion of Dr. Philip Levine, tests were carried out on the father's saliva to determine whether he was a secretor, and these tests proved that he was not.*

* The saliva was boiled and then centrifuged for 30 min. Two drops of the clear supernatant fluid were mixed with group O plasma of 1:30 titer. This mixture was allowed to stand at room

A résumé of the serologic findings in mother and infant is shown in Table I.

Autopsy findings: The body is that of an immature infant weighing 1290 gm. Skin and sclerae present a greenish hue. Pertinent findings in the viscera include a moderately enlarged spleen weighing 10 gm. Liver weighs 47 gm. On cut section minute yellowish foci are scattered throughout all the lobes. These foci average 1 mm. in diameter. Brain presents bright yellow discoloration of the medullary olives, of the cerebellar tonsils and vermis, and of the basal ganglia, claustrum, periventricular region of parietal lobes and hippocampal nuclei. Microscopically, foci of hematopoiesis are prominent in the liver and spleen. Bone marrow is hyperplastic. Numerous foci of coagulative necrosis are found throughout many portions of the liver lobules. Infiltration by acute inflammatory cells is noted in several of these foci. No necrotic changes in the ganglion cells are found in the brain. Final diagnoses: Congenital hemolytic disease with splenomegaly; extramedullary hematopoiesis of liver and spleen; kernicterus involving the cerebellar tonsils and vermis and of the basal ganglia, claustrum, periventricular region of parietal lobes and hippocampal nuclei; focal necrosis of liver.

TABLE I

	Dilutions made in saline		Dilutions made in alb.-plasma (A/P)		Anti A titer 1 part serum plus 2 parts blood group specific substance	
	Anti A	Anti B	Anti A	Anti B	Saline	Alb.-plasma
Mother's serum (12 days postpartum)	2,048	128	6,000	256	neg.	512
Baby's serum (postmortem)	neg.		9,000	—	—	4,096
Mother's serum (28 days postpartum)	2,048	4	1,024		neg.	4

Discussion

The criteria used in arriving at a diagnosis of congenital hemolytic disease in the three cases described in this report are: 1. Rapid onset of jaundice within 24 hours of birth. 2. Occurrence of anemia. 3. Presence of nucleated red blood cells in the peripheral smear. 4. Immunologic evidence of isoimmunization as determined by the high anti A agglutinin titer in the mother's serum. 5. Demonstration of circulating isoimmune bodies in the blood of the infant in the third case. 6. Typical anatomic findings of hemolytic disease as observed at autopsy. Although the degree of splenomegaly and hepatomegaly varied in these cases, the gross and microscopic findings are considered to be typical of the disease. The presence of extensive kernicterus in all cases also confirms this diagnosis since practically all cases of kernicterus observed have been associated with rather clear-cut clinical and autopsy findings of hemolytic disease of the newborn. As shown by Polayes and others, the titers of 1:10,120, 1:5,000, and 1:6,000 appear to be of a nature which would eliminate mere coincidence in these cases. In Case 2, the observation of megakaryocytoid cells in the hepatic sinusoids and the presence of marked eosinophilia of the portal triads and the splenic follicles are of importance in confirming the diagnosis.

temperature for 1 hr., and then 2 drops of a 4% suspension of group A cells were added. The mixture was then incubated at 37° for 30 min. and centrifuged for 1 min. Agglutination of the group A cells was estimated at 4 plus, thus indicating that the father was a nonsecretor. Three of 4 other group A individuals were found to be secretors.

Polayes has described these changes in cases of Rh isoimmunization.[9] In Case 2 additional weight for the proposed diagnosis of hemolytic disease is given by the occurrence of jaundice and anemia at birth as well as suggestive sequelae of kernicterus in the older sibling who also is a group A individual. In Case 1 the two other unaffected siblings belonged to group O and hence hemolytic disease would not be expected to occur in them. In Case 3 not only was there a markedly elevated anti A agglutinin titer observed in the maternal serum but also a similar antibody was found in the infant's serum. As can be seen from Table I none of the maternal anti A agglutinin active in saline was found in the infant's serum. Corroborative of the immune nature of the antibody circulating in the mother's serum was the fact that a titer of 512 was obtained in albumin-plasma mixture even after addition of one part of the mother's serum to two parts of A and B blood group specific substance. This finding is in agreement with a similar case reported by Witebsky[11] which he attributed to A-O isoimmunization. In his case as well as in the cases presented here complete neutralization of the saline-active antibody was obtained. He further demonstrated that the immune antibody, unlike the normal-occurring isoagglutinins A and B, fixed complement. In the present case such studies unfortunately were not carried out.

The term icterus precox has been used by Halbrecht to indicate a condition of less grave prognosis in individuals who have a moderate early jaundice and anemia caused by A-O or B-O isoimmunization. That A-B-O isoimmunization need not necessarily be associated with a benign course is illustrated by the present two fatal cases as well as by the two autopsies reported by Polayes and by Wiener.

In cases of this type the proper therapy should consist of immediate transfusion with group O, Rh positive blood to which the A and B blood group specific substances have been added, or by transfusion of washed, resuspended group O cells.

Summary

Three instances of fatal hemolytic disease of the newborn have been observed in group A infants born of Rh positive mothers belonging to group O. Markedly elevated anti A agglutinins were demonstrated in the mother's serum following delivery of the child. (1:10,120 in Case 1, 1:5,000 in Case 2, and 1:6,000 in Case 3. All these titers fell within three weeks.) All infants were Rh positive and no Rh or Hr antibodies were found in the mothers' serum. Jaundice became apparent in all infants within 24 hours of birth. There was a moderate anemia, and varying numbers of nucleated red blood cells were found in the peripheral blood. One infant died on the third day of life, the second on the fifth, and the third on the sixth. In all cases the typical changes of hemolytic disease of the newborn were present at autopsy and in all extensive kernicterus of the basal ganglia, hippocampal nuclei, periventricular pontine nuclei, cerebellar dentate nuclei and medullary olives were found.

The finding of free circulating antibodies in the infant's blood obtained postmortem is of particular interest. These anti A agglutinins were active only in albumin-plasma dilutions. The retention of the agglutinating property of this antibody in both infant and mother even after addition with A and B blood group specific Witebsky substances indicate that it is probably an immune antibody.

It is believed that A-O isoimmunization has been proved in these three cases.

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Spanish Abstract

Enfermedad Hemolítica Congénita que Resulta de Isoinmunización A-O

Se han observado tres casos de enfermedad hemolítica fatal de recién nacidos en infantes del grupo A nacidos de madres Rh positivo pertenecientes al grupo O. Aglutininas anti A marcadamente elevadas fueron demonstradas en el suero de la madre después del parto. (1: 10, 120 en Caso 1, 1:5000 en Caso 2 y 1:6000 en Caso 3. Todos estos títulos tocaron dentro de tres semanas.) Todos los infantes fueron Rh positivo y no se encontraron anticuerpos Rh o Hr en el suero de la madre. La ictericia se hizo aparente dentro de 24 horas después del parto en todos los infantes. Había una anemia moderada y se encontraron diferentes números de células rojas nucleadas en la sangre periferal. Un infante murió al tercer día de vida, el segundo al quinto, y el tercero al sexto. En la autopsia hubieron cambios típicos de enfermedad hemolítica del recién-nacido y se encontraron extensos kernicterus del ganglio basal, núcleos hipocampales, núcleos pontinos, nucleos dentados cerebelares y olivas medulares. Los descubrimientos de anticuerpos circulando libres en la sangre del infante después de su muerte son de particular interés. Estas aglutininas anti A fueron activas solamente en diluciones albumino-plasma. La retención de la propiedad de aglutinar de este anticuerpo tanto en la madre como en el infante después de al adición de las sustancias del grupo específico de sangre A y B (Witebsky) indica que es probablemente un anticuerpo immune.

Se cree que la isoinmunización A-O ha sido probada en estos tres casos.

Rockaway Parkway and Avenue A

INFANTILE CEREBRAL PALSY CASES WITH SEVERE MENTAL DEFICIENCY

Relationship of Etiology to Type of Neurologic Syndrome

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THE term "infantile cerebral palsy" is an all-inclusive one and, as generally used, refers to all types of motor defects resulting from cerebral abnormalities in which the causative factor was operative either before birth, at birth or during infancy. The relative importance of the various causative mechanisms in any large group of cerebral palsy patients will depend on certain associated factors. These include the average age at which the group is studied, the average degree of intellectual impairment and the relative distribution of the type of neurologic syndrome. It is the latter aspect, the correlation between etiology and the type of neurologic manifestation in infantile cerebral palsy, which forms the basis of the following presentation.

SUBJECTS

The group studied, numbering 157, included all the patients admitted to the Southbury Training School since its opening in 1940 in whom a diagnosis of infantile cerebral palsy was made. The average age of the group at the time of admission was 18 years; the average intelligence quotient, 25.

The clinical types of neurologic syndrome included the following 8 categories: spastic diplegia, paraplegia, hemiplegia, quadriplegia, triplegia, monoplegia, cerebellar ataxia and atonic diplegia. While all 4 extremities are involved in the spastic diplegias and quadriplegias, in the former the spasticity is more marked in the legs and is bilaterally symmetric, whereas in the quadriplegias the spasticity is asymmetric with equal or greater involvement of the upper extremities. The diagnosis of atonic diplegia was made on the basis of marked hypotonia and weakness of all extremities associated with hyperactive and equal deep reflexes and irregular plantar responses. Evidence of slight incoordination was rarely elicited, in contrast to the patients with cerebellar ataxia in whom hypotonia and weakness were minimal, with incoordination the major neurologic finding. The presence of athetosis did not influence the diagnostic category chosen and was found in the hypertonic plegic group as well as in the hypotonic ataxic group.

The etiologic diagnosis was made on the basis of available historical data obtained from parents, hospitals in which the births occurred, the physicians who delivered the children and complete clinical and laboratory studies. About 50% of the patients were delivered in hospitals and 70% of the remainder were attended by physicians in the home.

The diagnosis of birth trauma was confined to those patients with abnormally long, difficult or complicated birth histories who, in addition, had a history of a relatively stormy immediate postnatal period characterized by one or both of the following: 1. delay in initiation of respirations associated with continuous or intermittent cyanosis; 2. signs of central nervous system irritation, such as excessive drowsiness or convulsive phenomena. In a previous study of the asymmetric spastic palsies,[1] the relative reliability of these criteria for the diagnosis of birth trauma in older children was evaluated by an indirect method and found satisfactory.

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Six of the 8 patients whose cerebral abnormality was the result of maternal Rh isoimmunization have been reported in detail elsewhere.[3] The diagnosis was based on a neonatal history compatible with erythroblastosis fetalis, the proper Rh set-up in the blood of the mother and child and the presence of Rh antibodies in most of the mothers.

The undifferentiated group included all patients in whom no specific etiologic factors could be implicated. All of these cases were presumably congenital in origin. It was possible to rule out with reasonable assurance such prenatal conditions as irradiation of the mother, german measles or other known viral diseases in the mother during early pregnancy, infantile toxoplasmosis, congenital syphilis and significant prenatal trauma. A possible genetic basis was found in a number of instances as manifested by the presence of similar neurologic defects in one or more siblings or blood relations.

TABLE I

DISTRIBUTION OF PATIENTS ACCORDING TO ETIOLOGY AND NEUROLOGIC SYNDROMES

Type	Total	Birth Trauma	Post-infectious	Rh-Isoim-munization	Undifferentiated
A. Hypertonic					
Symmetric					
1. Diplegia	65				65 (2)
2. Paraplegia	7				7 (5)
Asymmetric					
1. Hemiplegia	41	8	5		28
2. Quadriplegia	20	3	4	7	6
3. Triplegia	1				1
4. Monoplegia	4	1	2		1
B. Hypotonic					
1. Congenital Ataxia	14			1	13 (6)
2. Atonic Diplegia	5				5
Totals	157	12	11	8	126 (13)

( )=Number of familial cases.

RESULTS

The results of the study are summarized in Table I. On the basis of muscle tone status, it was possible to divide the cases into a hypertonic and a hypotonic group. In the hypertonic group, no distinction was made between the increased tone due to pyramidal or extrapyramidal lesions. The clinical distinction is frequently unreliable and often both systems are involved. The hypertonic group can be further subdivided on the basis of neurologic signs into the symmetric and asymmetric palsies. The value of this division will be apparent when the etiologic factors are presented.

About 88% of the entire group showed increased muscle tone. Of the 138 cases in this group, approximately one half (72) exhibited bilateral symmetric involvement, and of these the majority showed diplegia. A little less than half of the hypertonic group (66 cases) showed irregular bilateral or unilateral involvement, the largest number being hemiplegics. Of the hypotonic group, three quarters exhibited ataxia as the predominant finding, the remainder being characterized by muscle weakness and hypotonia. Choreo-athetosis was present in 25 patients, distributed as follows: 12 in the spastic diplegias, 8 in the quadriplegias and 5 in the cerebellar ataxias. In the quadriplegic group, choreo-athetosis was found only in the cases resulting from maternal Rh isoimmunization.

As regards etiology, in the symmetric hypertonic palsies not a single case was found in which a specific natal or postnatal causative factor could be implicated. All were congenital in origin and presumably due to developmental defects of unknown origin. Of the 7 patients with paraplegias 5 were probably genetically determined since a similar neurologic defect was present in other siblings or blood relations. Two of the spastic diplegias were siblings. On the other hand, acquired

lesions (i.e., birth trauma or central nervous system infection) accounted for an appreciable proportion of the defects in the asymmetrically involved hypertonic group, namely 33%, being almost equally divided between the 2 factors. It is of interest that the relative importance of acquired lesions is about the same in the different clinical varieties of the asymmetric spastic group, that is, hemiplegia, quadriplegia and monoplegia. The cases resulting from Rh isoimmunization, however, are almost entirely confined to the quadriplegia group. In fact, it is the most important single etiologic factor in the patient with quadriplegia, accounting for 35% of the cases in this category. The only other manifestation of Rh isoimmunization in the cerebral palsy group was hypotonia with incoordination in one child.

In the hypotonic group about 70% of the patients exhibited ataxia as the primary disability. Except for the one case of Rh isoimmunization, all these patients had a congenital condition in which no definite causative factor could be implicated. That the developmental abnormality may be genetically determined in many of these patients is indicated by the fact that in six of them (46%) there was another sibling with a similar neurologic defect. In the patients with atonic diplegia, there was complete absence of any evidence of acquired abnormality.

For the group as a whole, the incidence of birth trauma was about 8%, and that of the postinfectious group 7% (2 cases of meningococcal meningitis, 2 cases of pertussis encephalitis and 7 cases of nonspecific, nonsuppurative encephalitis). The cases due to maternal Rh isoimmunization accounted for 5%. A total of 80% were considered developmental cerebral anomalies of unknown etiology and of these at least 10% were probably genetically determined.

Discussion

Although there is considerable expression of opinion in the literature as to the relative importance of the various etiologic factors in the infantile cerebral palsies, actual surveys of reasonably large groups have been reported infrequently. Moreover, the tendency to treat the cerebral palsy cases as a single group has made the evaluation and comparison of results difficult. The data here indicate the striking difference in etiology between the symmetrically and asymmetrically involved patients and the unreliability of interpretations based on unclassified cerebral palsy cases.

A state-wide survey in New Jersey by Phelps and McIntire[3] suggests another source of confusion in interpretation of etiologic factors, the average mental level of the group studied. In their series, a mental defect was found in only 25% of the group, the remainder of the patients being either of average or dull normal intelligence. However, the incidence of mental deficiency was twice as great in those who were considered to have developmental defects as in those diagnosed as birth injured. Since the group studied here represents exclusively cerebral palsy patients with marked degrees of mental defect, a much greater proportion of congenital defects is to be expected simply on the basis of selection.

While the incidence of developmental defects in this group as a whole approximated 80%, the importance of acquired defects in certain clinical classifications cannot be minimized. Thus, birth trauma and postnatal infection together were responsible for 31% of the cases of hemiplegia and for 35% of the cases of quadriplegia. The relative importance of Rh isoimmunization as the etiologic factor in 35% of the cases of quadriplegia must also be emphasized.

Summary

This is a report of a study of 157 cases of infantile cerebral palsy planned to demonstrate the correlation of etiologic diagnosis with neurologic residua. The average mental level of the group as a whole is represented by an intelligence quotient of 25, indicating the restricted distribution of the clinical material.

Birth trauma or postnatal central nervous system infections were found to be of etiologic importance in almost one third of the cases with asymmetric spastic involvement. On the other hand, these causative factors were not implicated in any of the hypotonic or ataxic group, nor in those spastic cases with symmetric involvement.

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Spanish Abstract

Casos de Parálisis Cerebral Infantil con Deficiencia Mental Severa Relación de Etiología al Tipo de Síndrome Neurológico

Este es un relato de un estudio de 157 casos de parálisis cerebral infantil planeado para demostrar la correlación de la diagnosis etiológica con el residuo neurológico. El promedio mental del grupo en conjunto está representado por un cociente de inteligencia de 25, indicando la distribución restringida de la materia clínica.

Se encontró que la truma de nacimiento o infecciones del sistema nervioso central postnatales eran de importancia etiológica en casi la tercera parte de los casos con complicación espática asimétrica. Por otro lado estos factores causantes no fueron implicados en ninguno de los grupos hipotónicos o atáxico, ni en aquellos casos espáticos con complicación simétrica.

Southbury Training School

RETROLENTAL FIBROPLASIA AND LIGHT

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THE disease retrolental fibroplasia was first reported in 1942 by Terry.[1] Since then the number of reports has increased, and concepts of the pathology have broadened. At first, embryonal connective tissue was thought to develop in the hyaloid artery system behind the lens.[2] Then the system of the vitreous was suspected.[3] Finally the retina itself has been demonstrated to be a site of the first pathologic changes.[4] The retinal changes described are, first, vascular engorgement, then edema, and then detachment of the retina and fibroplasia. Several observations would make it appear that the process may be more than ocular, in that it may involve the central nervous system and even the whole organism.[5] Many suggestions as to the etiology have been made, such as maternal vitamin A deficiency,[6] intrauterine viral infection,[5] toxicity of the maternal environment,[6] and the incomplete development of the premature infant influenced by neonatal environmental factors.[7] No conclusive evidence for any of these hypotheses has yet been demonstrated.[8–10] The one undisputed factor has been prematurity. The differing incidences at various institutions suggest postnatal factors and the one most strongly suspected is exposure to light.[10] Gamble[11] studied this factor in newborn rats by exposing their eyes to ultraviolet light. The young ones developed corneal bullae, corneal opacities and cataract, but no retinal changes.

In the present study the eyes of five infants of gestations ranging from 28 to 37 weeks and birth weights ranging from 1170 to 1350 gm. were covered from within a few hours of birth until a weight of 2000 gm. was attained. Cotton pads were placed over each eye and the pads held in position by a surgical stocking hood covering the head from the crown to the tip of the nose. From the strongest lamp used in the premature nursery, the maximum amount of light which can penetrate this protection is approximately 0.05 foot candle. On relatively rare occasions the shields were displaced by the movements of the infants, particularly as the infants grew older and more vigorous. However, displacement was unusual in the first three to four weeks and was vigilantly watched for and corrected by the nursing staff. No ophthalmoscopic examinations were made until the hood was finally removed.

The infants studied were all delivered in the Chicago Lying-In Hospital, cared for there in the premature nursery and then followed in the children's hospital of The University of Chicago. When ocular disease was suspected these infants were then examined by the ophthalmologists of The University of Chicago.

CASE REPORTS

Case 1. T.S. Father was 26 yrs. old and the mother 19 yrs. old. Pregnancy, which was the mother's first, was normal except for a natural onset of premature labor at 28 wks. Labor lasted 4 hrs. and delivery was by elective low forceps.

The infant weighed 1075 gm. at birth. His condition immediately after birth seemed good. He

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breathed immediately and spontaneously. He was given vitamin K (Hykinone) 4.8 mg. intramuscularly and was placed in an incubator continuously supplied with oxygen. His eyes were covered within 8 hrs. of birth. Eighteen hours after birth he began to have attacks of cyanosis which continued irregularly for 2 days. After this period he did well on a modified cow's milk formula. Forty cc. of whole blood were given by transfusion to correct an anemia of 8.5 gm. Hgb. Icterus was never clinically evident. The hood was removed from his eyes at 60 days of life. When 68 days old, he weighed 2530 gm. On this date it was noted that his eyes moved irregularly. Ophthalmoscopic examination revealed normal blood vessels on the retinae, and fetal pigmentation. There were no retinal detachments.

He was seen 3 wks. later because of poor weight gain and much flatus and regurgitation. It was noted then that his eyes moved irregularly and searchingly, but an ophthalmoscopic examination was not made. He was next seen when he was 4 mos. old and weighed 3150 gm. His mother then observed that his pupils were unequal. He enjoyed play and seemed to know his mother by touch and by voice. General physical examination revealed no abnormalities. The left pupil was small, irregular in outline and had no response to light. The tactile tension was increased. There was a green retinal reflex to light. Upon ophthalmoscopic examination the posterior chamber was found to be filled with an irregular green-white mass crossed by several tortuous blood vessels. The right eye had a moderately dilated round pupil which was fixed to light. The tactile tension was increased. The nasal, superior and inferior quadrants of the posterior chamber were filled with a green-white mass with a few irregular blood vessels over its surface. On the temporal quadrant of the retina the blood vessels were dilated and tortuous. The vessels appeared to project into the posterior chamber at various points. The diagnosis of retrolental fibroplasia was made. When seen again at 5 mos. of age, weight gain was adequate and progress generally was excellent. His eyes continued to roll aimlessly. Both posterior chambers at this examination were completely filled with green-white masses covered by a vascular network. There was no red reflex from any region of the retina.

Cases 2 and 3 are twins. The father was 36 and the mother 35 yrs. old. The mother had had two spontaneous abortions without dilatation and curettage. Four years previously she had undergone a cesarean section because of contracted pelvis after a 31 hr. labor. During this 4th pregnancy there was mild painless vaginal spotting at the 1st and 2nd mos., the 26th and 28th wk. of gestation. A diagnosis of placenta praevia was made then and twins were delivered by cesarean hysterectomy.

Case 2. K 1. Female, wt. 1300 gm. Condition immediately after birth seemed good and the onset of respiration was spontaneous and immediate. She was given vitamin K (Hykinone) 4.8 mg. intramuscularly and placed in an incubator constantly supplied with oxygen. The eyes were covered within 30 hrs. of birth. On the 2nd day of life severe pulmonary distress began with 2 episodes of cyanosis, presumably due to aspiration of mucus. There were no other cyanotic attacks and all signs of pulmonary disease had cleared after several days. Blood transfusions totalling 65 cc. were given for the correction of an anemia of 9.5 gm. Hgb. Icterus was never clinically evident. A modified cow's milk formula was used in feeding. The hood was removed when the child was 60 days old. Physical examination revealed no abnormality except that the eyes were moderately proptosed, the tongue prominent and the abdomen large and protuberant. No enlarged organs or masses were palpated. There was no heart murmur. A red reflex was obtained in each eye. The fundi were not examined in detail. The infant was discharged on the 63rd day of life weighing 2600 gm.

She was seen when 4½ mos. old. Then she weighed 4300 gm. The parents complained that the child had eaten very little. She was responsive to her parents, held up her head and smiled. The prominent tongue had regressed, but the abdomen had remained large. Head size was normal. Pupillary response to light was sluggish in each eye. Both retinal light reflexes were greenish-white. Fundus examination of the right eye revealed a superior retinal detachment elevated to plus 8 D. In the left fundus there were folds extending peripherally from the disc for a short distance. These were elevated 4 D. Engorged tortuous vessels were present in the region of the optic disc. Examination 9 days later revealed that the superior and inferior portions of the right retina were detached and elevated to plus 10 D. The retinal changes on the left were more marked. A diagnosis of bilateral retrolental fibroplasia was made.

Case 3. K 2. (Twin of Case 2) Female, wt. 1170 gm. Condition immediately after birth seemed good. Onset of respiration was spontaneous and immediate. She was given vitamin K (Hykinone) 4.8 mg. intramuscularly and placed in an incubator constantly supplied with oxygen. The eyes were covered within the first 30 hrs. of life. The neonatal course was not complicated by cyanosis or icterus.

Acyanotic apnea of short duration occurred occasionally during the 1st week of life. Blood transfusions totalling 65 cc. were given for correction of an anemia of 10.5 gm. Hgb. Feedings were based on a modified cow's milk formula. The hood was removed at 60 days of life. Like her twin (Case 2), this infant had a large abdomen and a protruding tongue. In addition, however, the spleen was enlarged 2 cm. and the liver was palpable 3 to 4 cm. below the costal margin. There were no heart murmurs. Her eyes were small and had constant searching movements. No retinal abnormality could be found by ophthalmoscopic examination. She was discharged at 2585 gm. when 75 days old.

She was seen again at the age of 4½ mos. The parents complained then that her eyes did not focus and that she was inattentive to light and to voices. Her weight was 3900 gm. Her head was peculiarly shaped and small. The interorbital distance was reduced and there was bilateral microphthalmos. The pupils reacted to light sluggishly but through a normal range. The retinal reflexes were bilaterally greenish-white. Ophthalmoscopic examination revealed green masses in both eyes. These masses were elevated from +4 to +10 D and had an occasional dilated blood vessel on the surface. The diagnosis of retrolental fibroplasia was made.

Case 4. B.R. Father was 23 and the mother 21 yrs. of age. This pregnancy was her first and was complicated by gonorrhea at the 25th week, preeclampsia and polyhydramnios. The pregnancy terminated at 33 wks. by a natural onset of a 4 hr. labor.

The infant weighed 1305 gm. and breathed spontaneously and immediately. His condition immediately after birth seemed good, but he had a congenital absence of the 5th toe and metatarsal on the left foot. The left leg was shorter and thinner than the right. He was given vitamin K (Hykinone) 4.8 mg. intramuscularly and was placed in an incubator continuously supplied with oxygen. His eyes were covered on the 1st day of life. Neonatal course was uncomplicated by cyanosis, apnea or notable icterus. He had a single unexplained rise of temperature to 39°C in the 3rd week of life, for which he was given penicillin intramuscularly. He gained well on a modified cow's milk formula. Blood transfusions totalling 40 cc. were given to raise the hemoglobin. The hood was removed from his eyes on the 36th day of life. He then weighed 2020 gm. Ophthalmoscopic examination revealed normal optic discs, vessels and retinae.

He was seen again when he was 4 mos. old and weighed 5760 gm. His parents had no complaints and said that he was quiet and easy to manage. It was said that he could smile but this was not seen at the examination. His head circumference was at the upper limit of normal. The eyes moved conjugately, but he did not follow a light or an object, although his mother and grandmother stated that he looked at various objects at home. The tactile tension of both eyes seemed normal. The pupils were equal in size and reacted well to light. The right optic disc was well outlined by a translucent area. This area was elevated 2 D and partially obliterated the normal red reflex in that region of the retina. The vessels in this area were dilated and tortuous. The left optic disc was normal. There was a retinal detachment with partial loss of the red reflex and several engorged, tortuous vessels in the superior temporal quadrant. In the superior nasal quadrant there were several engorged, tortuous vessels, but the retina was not detached. The superior nasal and temporal quadrants were roughly divided by a fold elevated to 2 D. This fold which was pigmented at its edges extended 5 disc diameters above the optic disc. Inferiorly and nasally there was a small retinal detachment with a three-quarter circle of pigment at its base. This area was about 1 disc diameter in size. The rest of the retina and the blood vessels appeared normal. A diagnosis of early retrolental fibroplasia was made.

Case 5. M. Father was 45 and mother 37 yrs. of age. This was the mother's 4th pregnancy. With this and with 2 previous pregnancies she was known to have hypertension. The pregnancy terminated with an uncomplicated labor of 57 min. at 37 wks. gestation. The pregnancy was complicated only by hypertension.

The infant weighed 1250 gm. at birth. She seemed vigorous. Onset of respiration was spontaneous and immediate. Vitamin K (Hykinone) 4.8 mg. were given intramuscularly and she was placed in an incubator continuously supplied with oxygen. A hood was placed over her eyes within the first 24 hrs. of life. The neonatal course was uncomplicated by apnea, cyanosis or icterus. A mild umbilical infection beginning on the 14th day of life subsided after 7 days' treatment with intramuscular penicillin. Transfusions totalling 50 cc. were given. Hemoglobin was 10.5 gm. The hood was removed on the 45th day. Physical and ophthalmoscopic examinations revealed no abnormalities. She weighed 2530 gm. when 56 days old. She was seen again at 4½ mos. of age. Then she weighed 4390 gm., was smiling and holding up her head, and recognized her mother by sight. Neither physical nor

ophthalmoscopic examination revealed any abnormality. She followed a light and bright objects with her eyes, and responded to changes in examiner's facial expression in an appropriate manner.

Discussion

The diet, the supportive measures and the exclusion of light were identical in the five infants studied. All received vitamin K, blood transfusions and modified cow's milk formula, and all were kept in incubators constantly supplied with oxygen. All received 15,000 u. of water soluble vitamin A as "Vipenta" by mouth daily from the 10th day of life to the present. Four children developed retrolental fibroplasia and one did not. Of the four involved, the twins were born after a gestation of 28 weeks complicated by repeated vaginal bleeding. One child was born after an uncomplicated pregnancy of 28 weeks. The fourth child was born after a pregnancy of 33 weeks complicated by pre-eclampsia and polyhydramnios. Two of the four affected infants were repeatedly cyanotic, but none had severe icterus. The head circumference of one infant was smaller than normal, and of another, larger. The latter infant also had a deformity of the left foot and lower leg.

Case 5 at age 4½ months, had no abnormalities in the eyes, even though her eyes had been covered for 45 days.

At the time of discharge from the premature nursery no defect was found in the eyes of the four infants who developed retrolental fibroplasia. Cases 1 and 3 who developed retrolental fibroplasia had irregular searching movements of the eyes when still in the premature nursery. These irregular movements were observed before there was any evidence of retinal change. Successive examinations of the four affected infants revealed abnormalities which were progressive. Retrolental fibroplasia is apparently a process which advances and which may not be a true congenital defect. It may be a congenital developmental defect, but even this is still not proved.

Summary

To discover whether exposure of the eye to light played any role in the pathogenesis of retrolental fibroplasia, the eyes of five premature infants were shielded for from 35 to 60 days after birth. Four of these five infants developed retrolental fibroplasia. One of the five infants developed no ocular abnormality of any kind. It is concluded that light is not an etiologic factor of retrolental fibroplasia in the premature infant.

Addendum

The possibility that premature exposure to light in premature children could be a factor in causing retrolental fibroplasia seemed obvious and was mentioned by a number of the early writers on the subject. In 1944 an experiment was made by Dr. R. C. Gamble and Dr. A. J. Strich, but was never published because the results were entirely negative. The basis for this investigation was the fact that most premature babies were put into special nurseries in which there were germicidal lights to prevent air borne respiratory infections and that the years during which these lights became commonly used corresponded well with the years in which the disease had its sudden increase in incidence. White rats were chosen because they are immature at birth and to some extent resemble premature babies. Families of these rats were raised in cages with varying exposures to germicidal light. The young rats were killed at varying ages and the eyes were removed and sectioned and examined microscopically. Keratitis, bullous degeneration of the cornea

and cataract were found in many of the eyes, but in no case was there any change in the retina or vitreous.—*Richard Gamble, M.D.*

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SPANISH ABSTRACT

Fibroplasia Retrolental y la Luz

Para descubrir si la exposición del ojo a la luz desempeñaba algún papel en el desarrollo de la fibroplasia retrolental, se les cubrieron los ojos a cinco infantes prematuros, cuyo peso era de 1075 gm. a 1350 gm. poco tiempo después del nacimiento hasta que alcanzaron un peso de 2000 gm. (35 a 60 días). Todos recibieron vitamina K, vitamina A como "Vipenta" 15,000 unidades diariamente, transfusiones de sangre para evitar anemia severa, y formulas de leche de vaca modificadas, y se mantuvieron en incubadoras con oxígeno la primera semana de vida.

Cuatro desarrollaron fibroplasis retrolental y uno no. Al tiempo de salir de la cuna prematura, no se encontró defecto en los ojos de los cuatro infantes que más tarde desarrollaron fibroplasia retrolental. Examenes succesivos de los cuatro infantes afectados revelaron anormalidades oculares progresivas. La fibroplasia retrolental es aparentemente un proceso que avanza y el cual pueda ser que no sea un defecto congénito. Pueda ser que sea un defecto de desarrollo congénito; pero esto no ha sido aún probado.

Se ha llegado a la conclusión de que la luz no es un factor etiológico de fibroplasia retrolental en infantes prematuros.

University of Chicago Medical School

ACUTE ISOLATED MYOCARDITIS

Review of the Literature and Report of a Case in a Ten Year Old Child

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ACUTE isolated myocarditis is the name given to a clinical syndrome in which the myocardium is the site of the pathologic changes, with a significant absence of accompanying lesions in the endocardium and pericardium. There is no known relationship to any of the infectious diseases. The disease is known by a variety of names, such as Fiedler's myocarditis, idiopathic myocarditis, acute interstitial isolated myocarditis, myocarditis of unknown etiology, productive myocarditis, pernicious myocarditis and eosinophilic myocarditis. Although first described by Fiedler[1] in 1899, the attention it has drawn is largely due to introduction of the subject into the American literature by Scott and Saphir[2] in 1929. Despite the fact that the disease is seemingly rare, case reports are increasing as the condition has become more familiar to both the clinician and pathologist.

For the most part, acute isolated myocarditis occurs either in infancy or in adults during the third and fourth decades. The 18 adult cases reviewed by Hansmann and Schenken[3] occurred in individuals from 21 to 57 years of age. In 1906, Forster[4] reported the first case in a child. At present the literature contains as many case reports of this condition in children as in adults. Stoloff[5] and Steiner and Bogin[6] first pointed out the apparent relationship of certain types of idiopathic cardiac hypertrophy in infants with acute isolated myocarditis. Since those publications, Maslow and Lederer,[7] Smith and Stevens[8] and many other observers[9–13] have reported instances of isolated myocarditis in children under the age of three years. Saphir[14] has made the interesting suggestion that many cases of so-called status thymico-lymphaticus with associated myocardial damage were most probably unrecognized examples of isolated myocarditis.

Despite the number of cases reported in the pediatric literature, there is a striking paucity of instances recorded in the older child. In a comprehensive review of the American literature, only two cases of this disease occurring in older children were found. Coulter and Marcuse[13] reported the disease in a 14 year old boy who died in three days. Saphir et al.[14] commented on its occurrence in a 10 year old Negro boy. Because of its apparent rarity in this age group, it was considered that the observed occurrence of another case should be recorded.

CASE REPORT

History: V.S., a 10 year old white Armenian girl, was admitted to the hospital in severe distress, with dyspnea, orthopnea and cyanosis. In her early childhood she had had rubeola, epidemic parotitis and pertussis. Tonsillectomy had been carried out without any known complications. Nothing suggestive of rheumatic fever could be elicited by careful questioning. Present illness began 3 days before admission when she first complained of slight upper abdominal pain. The next day the pain persisted

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and she vomited once. The day before admission a physician was called because of continued fever. He found no abdominal tenderness but, because of a slight cough, sulfadiazine was prescribed; a total of 3 gm. was taken. On the day of admission the cough was more hacking in type, temperature rose to 40.4°C. and following slight vomiting there was sudden development of respiratory difficulty that made immediate hospitalization imperative.

Physical Examination: On admission the child was in severe respiratory distress; her color was ashen grey with notable cyanosis of lips and nail beds. Respirations ranged between 80 and 110/min. with some suprasternal retraction. Temperature was 39.4°C. Pulse rate was about 140/min. and rhythm irregular. Heart sounds at the apex were weak, varying in intensity and partially obscured by the pulmonary signs. There was an evident pulse deficit although it could not be counted accurately. Point of maximum impulse was diffuse but the heart did not seem to be enlarged to a significant degree. Blood pressure was 80/50 mm.Hg. The vessels of the neck were prominent and

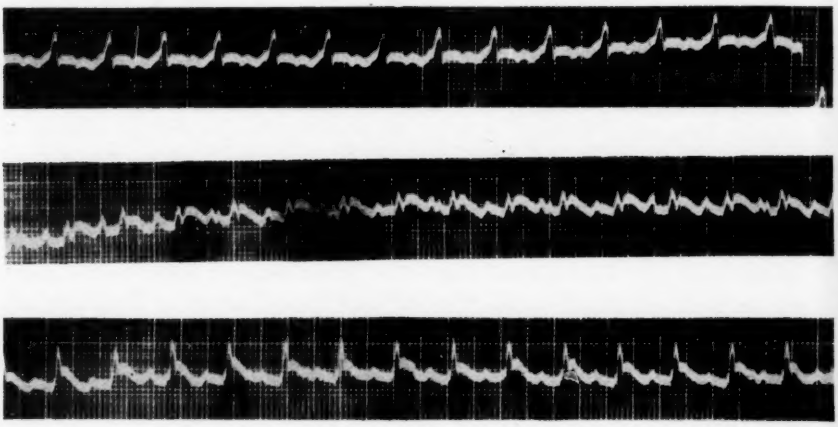

FIG. 1. Electrocardiogram taken 12 hrs. after admission (3 standard limb leads). Note elevation of ST segments in Leads 2 and 3.

the liver edge was felt 2½ fingerbreadths below the costal margin. Examination of the lungs revealed bubbling rales at both bases posteriorly, with crackling rales and a suggestion of bronchovesicular breathing low on the left side anteriorly.

Fluoroscopy showed a large area of density in the left lung field that was considered to be an area of consolidation involving either the lower part of the left upper lobe or the upper part of the lower lobe. The heart was noted to be approximately normal in size but the contractions were diminished in amplitude.

Course: On admission a diagnosis of pneumonia with cardiac failure was made. Penicillin 25,000 units intramuscularly every 3 hours was started after nose and throat and blood cultures were taken. The child was promptly placed in an oxygen tent and digalen was given intravenously (4 cat u.). Total calculated digitalizing dose of 9 cat u. was administered during the subsequent 24 hours. Small amounts of 50% glucose solution were given intravenously on several occasions. About 6 hours after admission, the cardiac rhythm became regular but the rate remained rapid.

Early on the following day, the patient seemed slightly improved with less respiratory difficulty; however, the cyanosis persisted even with oxygen therapy. Electrocardiogram revealed marked elevation of the ST segments in Leads 2 and 3 (Fig. 1). Variable crackling rales persisted at both bases and in the left axilla. A portable roentgenogram (Fig. 2) showed extensive bilateral bronchopneumonic changes and fluoroscopy demonstrated that the cardiac excursions still were small. Late in the day, the heart became obviously enlarged to percussion, dyspnea was more extreme and the patient became irrational.

On the 3rd hospital day, she was definitely worse with extreme restlessness, increasing dyspnea

and cyanosis. Physical findings included dullness to percussion as well as the crackling rales bilaterally in the lower half of the lung fields posteriorly. The heart rate remained between 120 and 140/min. and a gallop rhythm was noted. At no time were any murmurs or friction rub heard. Roentgenogram (Fig. 3) showed a marked spread of the pneumonic process and a definite increase of the heart size. Because of the rapidly increasing size of the heart with decreased pulsations of its borders and the electrocardiographic changes suggestive of pericarditis, a diagnostic pericardial tap was attempted but no fluid was obtained. That evening the patient suddenly became much worse; pulse was unobtainable and respirations irregular, and, despite emergency treatment, death occurred approximately 48 hours after admission.

Laboratory data: RBC count 5.7 million. Hgb. 14 gm./100 cc. WBC count 18 thousand. Adult polymorphonuclears 72%; immatures 15%; lymphocytes 13%. Urine normal; two nose and throat cultures negative for pathogens; two blood cultures sterile.

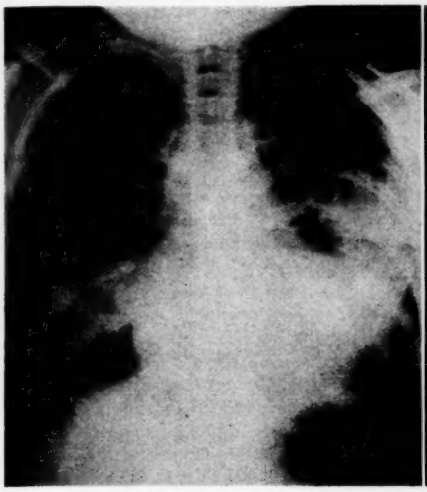

FIG. 2

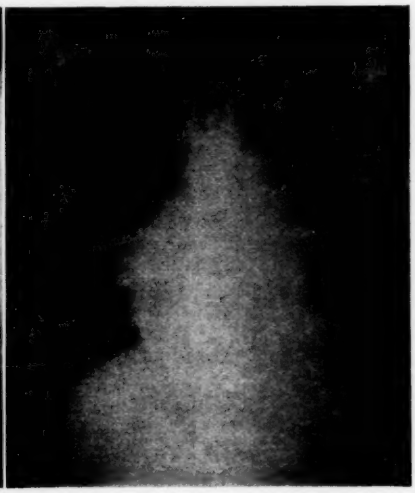

FIG. 3.

FIG. 2. Roentgenogram (bedside) taken 12 hrs. after admission. (Note bilateral pulmonary infiltration.)

FIG. 3. Roentgenogram (bedside) taken 36 hrs. after admission. (Note increase in size of heart and spread of congestive changes.)

COMMENT

The clinical impression was either a fulminating rheumatic process, with carditis and pneumonitis in the first attack or an overwhelming bacterial pneumonia (streptococcal or pneumococcal) with secondary cardiac involvement. The rapid course from the onset of symptoms to death with no rheumatic history or associated rheumatic manifestations and no definite clinical signs of endocardial or pericardial involvement made the rheumatic diagnosis unlikely. The second diagnosis of pneumonia, as the primary condition, seemed improbable because of the concomitant onset of pulmonary signs and the cardiac manifestations. As a rule, there is some delay in the appearance of signs of myocardial involvement and there usually are associated suppurative pleuritis and pericarditis. Negative nose and throat cultures also helped to rule out this diagnosis.

The possible relation of sulfonamide administration to the development of myocarditis was considered in this case. Such an instance had been reported by French and Weller.[15] The administration of sulfonamides by her private physician 48 hours after the onset of symptoms is of interest; however, it was not believed that the question of drug sensitivity played any role in this case.

Pathologic Findings

The body was that of a well developed and moderately well nourished white female. Neck veins were moderately distended. Skin and mucous membranes were pale.

Heart was enlarged, weighing 240 gm., and was flabby in consistency. Pericardium was normal. All chambers of the heart were dilated. The most significant change was present in the myocardium of the ventricles and the interventricular septum. Distributed throughout the myocardium and involving much of this tissue were irregular and ill-defined areas in which the normal appearance of the myocardium was lost. Most of these areas were yellow or yellowish tan in color; however, in some of the larger lesions were central linear red streaks. The change was more marked in the myocardium of the left ventricle and interventricular septum than in the right ventricular myocardium. In only a few small areas did the myocardial tissue appear entirely normal. Endocardium was normal. Valves were normal. Left ventricular myocardium measured 14 mm. and the right ventricular myocardium 3 mm. in thickness. Neither the foramen ovale nor the ductus arteriosus was patent. Coronary arteries were normal.

Left lung weighed 370 gm. and the right 400 gm. Pleurae were normal. Lower lobes of the left lung and the inferior portion of the upper lobe were congested and edematous. The surface exuded a frothy blood tinged fluid. Right lower and middle lobes and the inferior portion of the right upper lobe had the same appearance. No organisms were obtained from the lung cultures.

Other organs and tissues were normal.

Microscopic Examination

Heart.—Sections of heart examined are obtained from the right and left ventricles, interventricular septum, right and left auricles, aortic and mitral valves. Changes observed in the sections from the right and left ventricles and interventricular septum vary only in degree both within the same location and in the various anatomic locations; therefore, a single description will suffice. In every section there is mild to marked inflammatory reactions present in the interstitial tissue of the myocardium (Fig. 4). This infiltration consists of a large number of lymphocytes, a few to moderate number of eosinophilic and neutrophilic leukocytes, large mononuclear cells and a rare plasma cell (Fig. 5).

Only in those areas where the inflammatory process is most severe is there degeneration of muscle fibers. In these areas, neutrophilic leukocytes are present in slightly greater numbers than elsewhere. In the hematoxylin and eosin stained preparations, degeneration of muscle fibers is not conspicuous, being much less than one would expect considering the marked inflammatory reaction. However, the phosphotungstic acid hematoxylin stain demonstrates focal areas in which there is a moderate to marked degeneration of these fibers (Fig. 6). A mild to moderate infiltration of inflammatory cells is present about some of the coronary arteries and veins. This reaction does not involve the vessel wall nor does it in any manner resemble that found in rheumatic heart disease. Throughout the myocardium there is a moderate degree of interstitial edema. Granulomatous lesions are not present.

The myocardial inflammatory reaction in some areas extends to the epicardium, and in several small foci there is a mild cellular infiltration of this tissue adjacent to the myocardium. Some of the sections from the right and left auricles reveal interstitial edema and an extremely mild focal infiltration of lymphocytes. The valves are normal.

No organisms could be demonstrated in the tissue with Giemsa, Ziehl-Neelson, Steiner and Brown-Breen stains.

Lungs.—Alveoli are filled with edema fluid and red blood cells. Capillaries of the alveolar walls are congested.

Adrenals.—In the periadrenal tissue is a minute adenoma that has been almost completely destroyed as a result of hemorrhage into its substance.

Thymus.—The cortico-medullary architecture is ill-defined but the cellular components are normal.

The ovaries contain several small follicular cysts.

All other tissue examined is normal.

Discussion

The etiology of acute isolated myocarditis is as obscure today as it was when the disease was originally described. Among the diseases that most commonly cause myocarditis, rheumatic fever has been ruled out as causative agent because of the absence of specific pathologic lesions. The possibility of infectious diseases such as diphtheria, pneumonia,

and scarlet fever that may be complicated by myocarditis can be excluded by history and lack of clinical signs of such disease. Some investigators have favored the theory of sensitivity to chemicals such as adrenalin, bismuth, sparteine and sulfonamides. French and Weller[15] reported a case of myocardial inflammation secondary to sulfonamide administration. That a hypersensitivity basis is conceivable is further substantiated by the recent work of Gregory and Rich[16] who produce similar myocardial lesions by sensitizing guinea pigs to horse serum, streptococcal products and powdered egg albumin, by the occasional finding of a predominantly eosinophilic infiltration, and by the occasional presence of isolated myocarditis in an eczematous infant (Bernheim-Karrer).[17] Toxemia

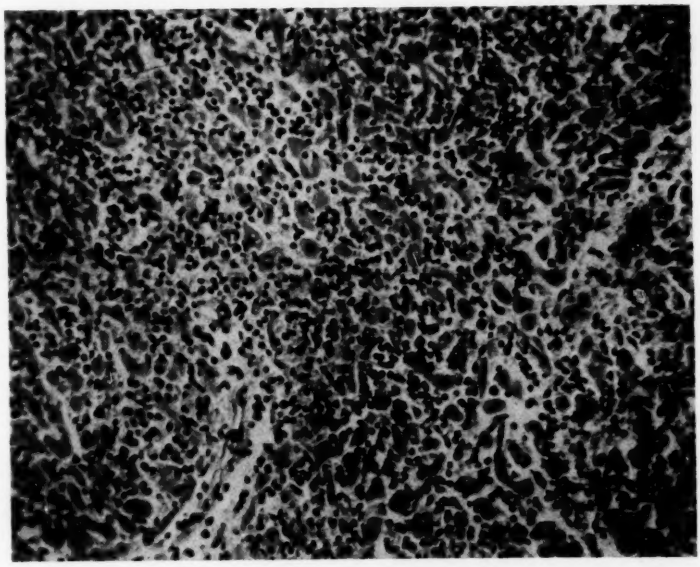

FIG. 4. Inflammatory reaction of moderate degree in myocardium. Infiltrating cells are lymphocytes, eosinophilic and neutrophilic leukocytes, large mononuclear cells and rare plasma cell H. and E. × 260.

of an unknown nature and viral agents have been considered. To date, neither has been completely excluded.

The heart is enlarged and dilated. Neither the pericardium nor the endocardium is abnormal. The myocardium is generally pale gray with occasional areas of yellow alternating with gray streaks. The histologic findings are not specific. The disease, as originally described, was solely an acute interstitial myocarditis but it is now accepted that varying degrees of muscle fiber degeneration may also be present. The infiltration is usually diffuse. The cellular elements are not characteristic; they are chiefly lymphocytes and large mononuclear cells with occasional neutrophilic and eosinophilic leukocytes. Infrequently, the cells are present in the perivascular tissue but are not arranged in the characteristic rheumatic pattern. Saphir[14] describes the rare occurrence of granulomatous formations characterized by areas of necrosis of myocardial fibers surrounded by the cellular elements mentioned above, and, in addition, the presence of occasional multinuclear giant cells. This granulomatous reaction was present in one out of his 15 cases.

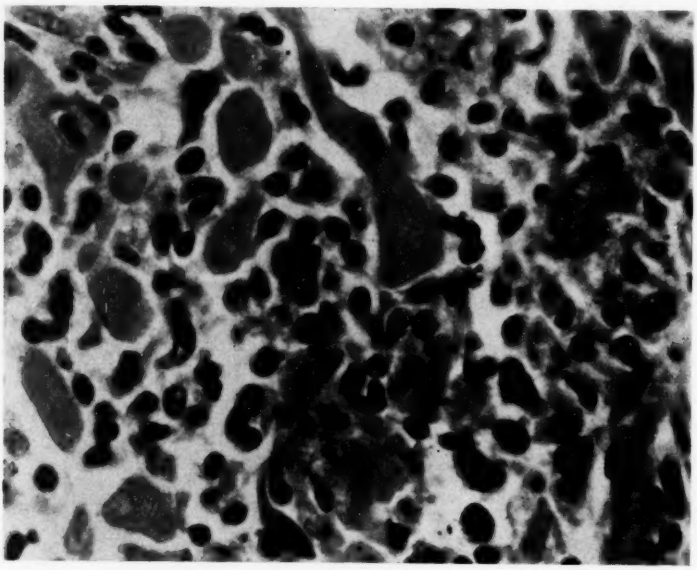

FIG. 5. Section of left ventricle, various types of inflammatory cells in myocardium. Some of muscle fibers are degenerating. H. and E. × 1000.

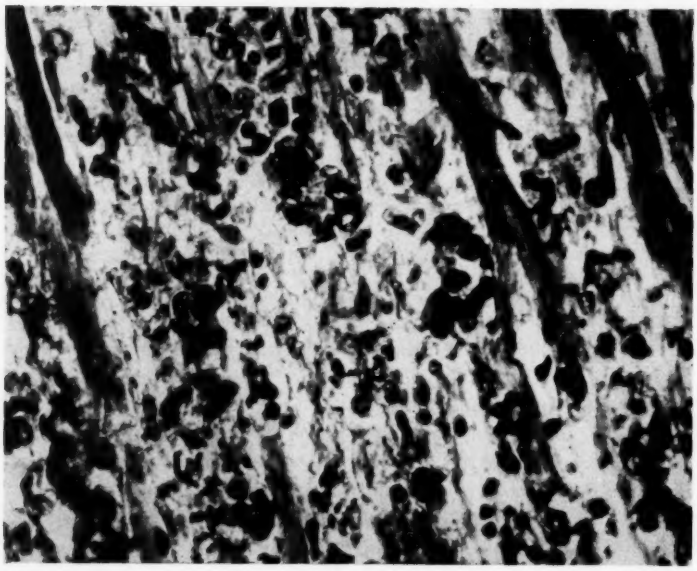

FIG. 6. Section of interventricular septum. Area of marked degeneration of myocardial fibers together with inflammatory infiltrate. Phosphotungstic acid and hematoxylin stain. × 660.

The diagnosis of acute isolated myocarditis is most difficult to establish clinically. The picture is that of progressive myocardial failure. The usual mode of onset is sudden with precordial distress, palpitation, restlessness, increasing dyspnea and cyanosis. Seventy per cent of the cases reviewed by Hansmann[3] had fever of varying severity. The physical findings include cyanosis, tachycardia out of proportion to the temperature, cardiac arrhythmia, progressive enlargement of the heart, manifestations of pulmonary edema and hepatomegaly. Only 14% of this series had peripheral edema.

The course varies in duration from three days to several months with death usually occurring suddenly. It is of interest that all three cases in the age group under consideration had a similar picture of acute onset with a brief course terminating in death in less than a week.

The diagnosis may be suspected clinically in an individual with the symptoms and signs of rapidly progressing myocardial failure, in the absence of a past history or present manifestations of rheumatic fever or of infectious diseases known to be associated with myocardial involvement. A definite diagnosis can only be made by postmortem examination.

Summary

A brief review of the literature on acute isolated myocarditis is presented. The age incidence of reported cases is predominantly in two groups, adults and infants or children under the age of three years. A case of a 10 year old child who ran a rapid, six day course terminating in death is reported with postmortem findings. Diagnosis of acute isolated myocarditis may be suspected clinically but can be made with finality only with postmortem examination.

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SPANISH ABSTRACT

Miocarditis Aislada Aguda
Análisis de la Literatura y Relato de un Caso en un Niño de Diez Años de Edad

La miocarditis aislada aguda es un síndrome relativamente raro de etiología desconocida, en el cual el miocardio es el asiento de los cambios patológicos, con la ausencia completa de la afección del endocardio y del pericardio. La característica principal es la apariencia rápida de signos y síntomas de la falta de funcionamiento miocardial en la ausencia de historia previa y las manifestaciones presentes de la fiebre reumática o cualquier otra enfermedad infecciosa que se sepa estar asociada con el daño miocardial. El curso es corto, generalmente termina en la muerte en un período de tres días a varios meses. La enfermedad ocurre por lo general en niños jóvenes o en adultos en la tercera y cuarta décadas. Se han visto pocos casos en niños mayores. Se presenta un caso de una niña de diez años de edad que vivió seis días después de que le principiaron los síntomas. Se dan los descubrimientos después de la muerte. La diagnosis de la miocarditis aislada aguda se puede sospechar sólo clínicamente. La diagnosis definitiva se puede hacer por la correlación de descubrimientos microscópicos después de la muerte con las características clínicas.

3 East 71st St.

MENINGOCOCCEMIA WITH MENINGITIS ACCOMPANIED BY BILATERAL GANGRENE OF THE LOWER EXTREMITIES (WATERHOUSE-FRIDERICHSEN SYNDROME)

By CHARLES P. DEFUCCIO, M.D., AND EVELYN E. DRESNER, M.D.
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THE term "Waterhouse-Friderichsen" syndrome has been used to denote the disorder of fulminating meningococcemia accompanied by adrenal hemorrhage and shock. The syndrome consists of cyanosis, petechial and purpuric rashes, which may coalesce into large ecchymotic areas.

This case is reported because recovery from the Waterhouse-Friderichsen syndrome is uncommon and gangrene accompanying meningococcemia is rare.

CASE REPORT

History: H. K., a 7 yr. old Negro boy, was admitted to the Medical Center of Jersey City with the chief complaint of fever and headache. The child had been well apparently until the evening prior to admission. He then began to complain of a headache and had fever. On the morning of admission he vomited once, went to sleep and could not be roused. Past medical and family history were noncontributory.

Physical examination revealed a well developed boy who was semicomatose, lying in bed with both knees flexed and with his head slightly extended. Head was normal symmetrically and showed no bruises. Both pupils were equal and reacted to light. There were multiple petechiae on the conjunctivae of both eyes. Ears, nose and throat were essentially normal. Neck was markedly rigid. Lungs were clear to percussion and auscultation. Radial pulse was weak. Blood pressure was 68/50 mm.Hg. Abdomen was slightly rigid. No masses were palpable. Liver, kidney and spleen were not palpable. Active peristalsis was present. There were multiple, small nonelevated areas of pigmentation over the trunk and extremities. Reflexes were active. Kernig's and Brudzinski's signs were positive.

Provisional diagnosis on admission was meningococcemia with meningitis and Waterhouse-Friderichsen syndrome.

Hospital course and treatment: Initial lumbar puncture revealed clear spinal fluid, not under increased pressure. No organisms were found on smear and culture of this initial spinal fluid. However, culture of the spinal fluid taken 5 days later was positive for M. meningococcus. A blood culture taken on admission was positive for M. meningococcus.

He was given penicillin 20,000 units intrathecally, instilled in the spinal canal at the time of the initial lumbar puncture. Penicillin 300,000 u. was given daily by continuous intramuscular drip. Sulfadiazine, 0.7 gm., was given every 4 hrs. Adrenal cortical extract (desoxycorticosterone acetate, "Doca" Roche) was given in doses of 1.0 cc. every hr. for the first 4 days, and the dose then decreased to 1.0 cc. every 2 hrs. The dose was given less frequently as the blood pressure began to mount. The child received transfusions of blood and general supportative treatment as needed.

Twelve days after admission, the blood pressure had risen to 98/80 mm.Hg. He had edema of both eyes, hands and ankles. Toes of both extremities were black and cold. Multiple bullous lesions appeared on the ankles (Fig. 1). Direct smear taken from these blebs showed the presence of M. meningococcus. Fluid from the blebs showed a positive precipitation reaction with Type 2 antimeningococcal serum.

Three days later, he was well oriented. Blood pressure was 100/80 mm.Hg. Gangrene of the toes was becoming more marked (Fig. 2).

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(Received for publication Sept. 17, 1948.)

Gangrene of the toes continued to progress and a week later there was a definitely demarcated, dry gangrene of the left foot, involving the toes and sole of the foot, and an undemarcated wet gangrene of the right foot (Fig. 3).

Bilateral amputation, at the lower third of both legs, was performed a month later. (Fig. 4).

At present the child is in good health and normal in mental and physical development. He is being prepared for prosthetic limbs.

DISCUSSION

Reference to skin and toe gangrene was found in only a few cases in the recent literature dealing with meningococcal septicemia. One case was reported by Bernstein[1] with the syndrome of causalgia, and another was reported by Hayes and Whalen.[2] Smith et al.[3] reported a case of meningococcemia with gangrene in which amputation was necessary.

In spite of the purpura, the petechiae and the lowered blood pressure, there was some hesitancy in calling this a Waterhouse-Friderichsen syndrome, since Martland[4] states that cases of meningococcemia, with or without meningitis plus massive hemorrhages into the adrenal, never recover, regardless of any treatment. However, he does mention that in some cases of meningococcemia, purpura, petechiae and cardio-respiratory collapse with recovery may be found.

SUMMARY

A case of meningococcemia with meningococcal meningitis, complicated by gangrene of the lower extremities, is reported. Amputation of the lower third of both legs was performed. The patient is living and in good health.

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SPANISH ABSTRACT

Meningocemia con Meningitis Complicada de Gangrena de las Extremidades Inferiores ("Sindrome de Waterhouse-Friderichsen")

El término "Síndrome de Waterhouse-Friderichsen" ha sido empleado para indicar un estado de meningocemia fulminante acompañada de hemorragia de la glándula suprarrenal y de shock. El síndrome consiste de cianosis, erupción de petequias y púrpura, que coalescen en extensas áreas equinóticas.

Se describe un case de meningocemia con meningitis meningocócica, complicada de gangrena de las extremidades inferiores, porque (1) la recuperación del "Síndrome de Waterhouse-Friederichsen" no es común y (2) porque la gangrena asociada a la meningococemia es muy rara.

Se hizo la amputación del tercio inferior de ambas piernas. El enfermo sobrevivió y se encuentra en buena salud.

Jersey City Medical Center

FIG. 1. Extensive ecchymotic areas and bullous lesions.

FIG. 2. Definite areas of gangrene.

FIG. 3. Areas of gangrene with sloughing.

FIG. 4. After amputation.

BRAIN TUMORS IN CHILDREN

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THE most common varieties of neoplasm encountered in pediatric practice are tumors of the brain and spinal cord, tumors of lymphoid tissue (for example, sarcomas, Hodgkin's disease), malignant bone tumors and embryoma of the kidneys.[1] It is generally considered among members of the medical profession that brain tumors, particularly in children, offer a serious prognosis. This is, of course, doubly true in the sense that brain tumors not only may be malignant in themselves, but may become a serious threat to life because of their location. It must be pointed out, however, that the other common tumors—sarcomas, Hodgkin's disease and malignant bone tumors—are almost invariably fatal and that embryoma also offers an exceedingly grave prognosis.[2]

During the past three decades many advances have been made in neurosurgery, neurology and neuropathology. The study of brain tumors was advanced greatly by Cushing[3] and his pupils and in children in particular by Bailey and others.[4] It has become apparent that the diagnosis and treatment of brain tumors is dependent on the cooperation of experts working in closely allied fields. The pediatrician must become alert to detect the early signs of tumor and must be prepared to call on the neurologist, the ophthalmologist and the roentgenologist to aid in accurate diagnosis, thus giving the neurosurgeon the earliest possible chance to carry out successful therapy. The latter is greatly aided by the neuropathologist in making decisions as to the type and extent of treatment at the time of operation. Finally, the radiologist may be necessary in carrying out the postoperative radiotherapy.

In an attempt to review the results of such cooperation the records of 606 children aged less than 15 years, including all those observed at the Mayo Clinic from 1907 (the earliest record available) through 1946, have been studied. Record has been made of 1. the various types of tumor that occur and their incidence, 2. the location of the tumors and 3. the outcome in those patients who survived for a shorter or longer time, in an attempt to see how these statistics compare with those previously reported. In this group, 427 tumors were verified histologically from tissue removed at operation or necropsy. The interpretation in all cases has been reviewed and recorded by one of us (J. W. K.). In 73 cases, the presence of a tumor was verified by the surgeon but no tissue was obtained for further study. In 106 cases no tumor was found at operation, nor was exploration undertaken, and no information could be obtained as to subsequent events. These latter two groups of cases have not been included in this series.

Three hundred and fifty-nine of the verified tumors in children were gliomas (84%). In 1932 Cushing[3] found that 42.6% of all brain tumors in children and adults were gliomas. Elvidge and others[5] found that 44.9% of their series of 467 verified tumors of

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the brain and cord were gliomas. Baker[6] gave 61.8% of his series as gliomas and Bennett[7] reported 62.9% of the primary intracranial neoplasms observed at the Army Institute of Pathology as gliomas. This last group included only persons from 18 through 38 years of age. In 1942 Smith and Fincher[8] reported that 86% of 87 verified tumors in children were gliomas. This corresponds closely to our figure of 84%.

Astrocytoma was the most frequent tumor, being present in 24.4% of the cases. Medulloblastoma was a close second, being present in 20.1%. Ependymoma was present in 11.4%, glioblastoma multiforme in 9.3% and craniopharyngioma in 5.4%. All other tumors together constituted 29.4%.

This study is concerned with determining whether the incidence of certain tumors was more or less in the younger children, that is, during the first five years of life. Astrocytomas occurred in about the same proportion in both the group from birth through 5 years of age (27%) and the group from 6 through 14 years of age (24%). Medulloblastomas were somewhat more common in the younger group (24%) than in the older group (19%). Ependymomas were also somewhat more common in the younger group (17%) than in the older group (10%). Glioblastomas were considerably less common

TABLE 1

LOCATION OF TUMORS

Ages of patients	Total	Infratentorial		Supratentorial	
		Number	Per cent	Number	Per cent
Birth—5 yr.	108*	77	71	30	28
6–14 yr.	319	204	64	115	36
Total	427	281	66	145	34

* One tumor was both supratentorial and infratentorial.

in the younger group (5%) than in the older group (11%). The more rare types of tumor were rather more common in the older group than in the younger group.

It is well recognized that infratentorial tumors are more common in children than are supratentorial tumors. In this series, 66% of all tumors were infratentorial and 34% were supratentorial. This is in almost exact agreement with Cushing's figures (quoted by Ford[9]) for children less than 15 years of age (65%). The percentages of infratentorial and supratentorial tumors in children from birth through 5 years and from 6 through 14 years are given in Table 1.

Two hundred and eighty-one tumors were infratentorial. Of these infratentorial tumors, 85 (30%) were astrocytomas and 84 (30%) were medulloblastomas. There were 35 ependymomas (12%) and 19 cases of glioblastoma multiforme (7%). There were 58 other tumors of less common types (21%).

One hundred and forty-six tumors were situated above the tentorium cerebelli. One of these tumors also extended below the tentorium. There were 23 craniopharyngiomas (16%), 18 astrocytomas and 18 cases of glioblastoma multiforme (each 12%), 13 ependymomas (9%), 10 pituitary adenomas (7%) and 64 other tumors (44%).

Six tumors were found in infants 1 year of age or less. A sarcoma or meningioma was removed from a baby aged 2 months, who survived the operation for 10 days only. A perivascular fibrosarcoma which was both intracranial and intraorbital was successfully

removed from a boy aged 2 months, who was reported as well four months after operation. A meningioma of the choroid plexus was removed from an infant aged 7 months, who survived the operation for three months. In a boy aged 10 months a cerebellopontine ependymoma was found, but the child died before operation could be attempted. There were two infants, each aged 1 year, one of whom had a medulloblastoma and one an astrocytoma. Neither infant survived operation for more than 12 days.

Roentgenograms without air injection have proved of considerable value in indicating the presence of a brain tumor. In a series of 384 of these cases in which roentgenograms were studied, the findings indicated the presence of tumor in 267 (69.5%). The following findings were suggestive of, or indicative of, intracranial tumor: 1. separation of sutures; 2. erosion of the clinoid processes; 3. erosion of the floor of the sella turcica;

TABLE 2

BRAIN TUMORS IN CHILDREN: SURVIVAL RATES

Period yrs.	Patients*		Lived 6 mos. or longer		Patients traced	Lived 1 yr. or longer		Patients traced	Lived 5 yrs. or longer	
	Total	Traced	Number	Per cent of traced patients		Number	Per cent of traced patients		Number	Percent of traced patients
1920–1924	23	21	5	23.8	20	2	10.0	19	1	5.3
1925–1929	77	73	17	23.3	71	14	19.7	68	8	11.8
1930–1934	73	70	24	34.3	70	20	28.6	65	4	6.2
1935–1939	93	89	46	51.7	85	37	43.5	70	15	21.4
1940–1944	108	94	51	54.3	81	34	42.0	34	6	17.6

* Inquiry as of Jan. 1, 1947. Included in the 5 yr. group are only those children who underwent operation in 1941 or earlier.

4. abnormal areas of calcification; 5. erosion of, or lateral thinning of, areas of the frontal, occipital or parietal bones.

There is no question that a brain tumor is a serious lesion. This is inevitably so because of its situation, and frequently this factor alone prevents adequate surgical treatment. In addition, as is well known, many tumors are not encapsulated but infiltrate the soft tissue of the central nervous system readily and widely. It is of great interest, especially to the general practitioner and the pediatrician, to know the ultimate outcome, that is, the chances for survival and for cure of any individual patient. There are many factors which affect the prognosis, of course, and to enter into detailed discussion of them all is not the purpose of this study. To obtain an over-all picture the series was divided into five year groups (as to date of operation) and found that under present-day conditions approximately 54% live for six months or more. In the period 1920 through 1924, only 23.8% lived six months or more; from 1925 through 1929, 23.3%; from 1930 through 1934, 34.3%; from 1935 through 1939, 51.7%; from 1940 through 1944, 54.3% (Table 2). These include all types of tumor and the higher percentage in recent years probably represents earlier and better diagnosis and improved surgical management.

In studying survival of patients who have malignant disease it is customary to consider a five year period as a satisfactory interval for observation. In the 25 years from 1920 through 1944, 374 patients were treated, and 256 of them were traced at the end of five years. Of these traced patients, 34 (13.3%) lived five years or longer. It will be seen, by referring to Table 1, that, in any one selected period, from 1 to 15 patients survived for five years or more, that is, from 5.3% to 21.4% of the patients traced. Many of them lived seven, eight or nine years and of course had a further life expectancy.

The largest number of these 34 patients who lived five years or more had astrocytoma (13 patients). Six had craniopharyngioma and three had ependymoma. Other diagnoses in this group were two cases each of astroblastoma, chromophobe adenoma of the pituitary, oligodendroglioma, ganglioneuroma and meningioma, and one case each of xanthoma and cavernous hemangioma.

Eight patients were alive 10 years or more after the initial operation. A short discussion of each of these patients may be of interest.

Report of Cases

The patient who lived the longest was alive and well 20 years after the removal of a cystic astrocytoma involving both cerebellar lobes. The cyst had been aspirated on several occasions before operation and temporary relief of symptoms had been produced. An extensive multilocular cystic tumor was enucleated, including a small nodule from the 4th ventricle. Fifteen years after this operation, exploration of the cerebellum was again carried out and a section of thin membrane between the wall of the cyst and the 4th ventricle was removed. The patient has remained well since that time.

A patient, who had had a meningioma removed, was alive but ill 16½ years after operation. The tumor was rounded, weighed 110 gm., measured about 8 cm. in diameter and was attached to the dura. Six years later the patient had epileptiform convulsions and still later nearly complete blindness. When last heard from (1942) she had been in a delirious state for 4 days. This was described as "an hysterical type of psychosis."

Another patient was alive and well 18 years after removal of an ependymoma of the right parietal lobe. This appeared as a large cyst containing 120 cc. of yellow fluid. A small nodule of tumor was found on the median wall of the cyst and was removed. Six years after operation, left-sided convulsions developed. These were well controlled by means of ketogenic diet and medication. At the last report the patient was well, had married and during pregnancy had a recurrence of "tingling sensations" but no convulsions.

A patient, aged 7 years, had a cystic oligodendroglioma of the left cerebellar lobe. The tumor was large and filled the 4th ventricle. It was removed piecemeal and the base was cauterized on the mesial aspect of the left cerebellar lobe. There was cystic arachnoiditis around the tumor and yellowish fluid, which clotted on standing, was aspirated. This patient had had a history of occasional headaches for 2 weeks only before examination. She has been well for the 13 years since operation.

A boy, aged 9 years, had a meningioma arising beneath the optic chiasm, and had had gradual loss of vision for 2 years but no other symptoms. Through a transfrontal craniotomy the tumor was enucleated. It was found to be 4 cm. in diameter. The patient remained comparatively well for 13 years. His vision recovered for a time but then failed slowly. He remained small in stature and was about 150 cm. tall and about 43 kg. in weight at the age of 22 years. He gradually became clumsy, his speech slurred and he died 16 years after operation, undoubtedly with a recurrence of the tumor.

A boy, aged 10 years, underwent removal of a craniopharyngioma. Sixteen years later he presented himself for treatment in another city. He had had headache and vomiting for 4 years before the removal of the tumor and bitemporal hemianopia was present. The tumor arose from the area of the sella turcica and extended posteriorly beneath the chiasm. Intracapsular removal of a mass of calcareous-cholesterol material was carried out. The capsule was left in situ.

A boy, aged 8 years, had complained of failing vision and headaches for 2 months. His vision was greatly reduced in both eyes. Through a transfrontal craniotomy, a tumor was found beneath the optic chiasm and intracapsular removal carried out. The tumor was diagnosed as a chromophobe

adenoma of the pituitary gland. When the patient was last heard from 12 years later, his condition was good, although he was blind. He had had no further treatment.

A boy, aged 13 years, had an ependymoma situated in the midline beneath the inferior poles of the cerebellar lobes. The tumor was pyramidal in shape, extended into the 4th ventricle and was found to be cellular and vascular. Biopsy was done but the tumor was not removed. Postoperative roentgen therapy was given over the posterior fossa on 3 occasions. About 18 months later the patient was able to walk and his general condition was reported to be fairly good. Ten years later he began to have nocturnal convulsions, with some headaches and buzzing in his ears. Eleven years after the original biopsy and decompression, re-exploration of a bulging cerebellar mass was undertaken. A subarachnoid cyst was incised, beneath which the extensive tumor was found filling the 4th ventricle and extending upward into the 3rd ventricle. Resection was out of the question, and the patient died the following day. It is of interest that this patient lived a comfortable life for 11 years after decompression and roentgen therapy.

Summary

Twenty-four per cent of brain tumors of children aged less than 15 years were found to be astrocytomas, 20% were medulloblastomas and 11% were ependymomas. If the astroblastomas (3%) and ependymoblastomas (3%) are added to these, these groups of tumors comprise 61% of all brain tumors of children. Gliomas constituted 84% of all the tumors in children.

Six tumors were found in infants 1 year of age or less. The youngest infants were 2 months old.

Astrocytomas were slightly more common in children aged 5 years or less than in the older group. Medulloblastomas and ependymomas were distinctly more common in the younger group than in the older group.

Seventy-one per cent of tumors in the age group from birth through 5 years of age were infratentorial; 28% were supratentorial; 1 tumor (1%) was both infratentorial and supratentorial. In the group 6 through 14 years of age, 64% were infratentorial and 36% were supratentorial. Thirty per cent of infratentorial tumors were astrocytomas and 30% were medulloblastomas. Sixteen per cent of supratentorial tumors were craniopharyngiomas, 12% were astrocytomas and 12% were glioblastoma multiforme.

Under present conditions at the Mayo Clinic, 54% of all children who undergo operation for tumor of the brain survive for six months or more. Of 256 patients observed for five years or more after operation, 13.3% survive for at least five years. The longest survival period was 20 years after operation. This patient had had an astrocytoma removed in 1926.

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SPANISH ABSTRACT

Tumores del Cerebro en los Niños

Se presenta un análisis de 427 tumores del cerebro comprobados mediante el estudio histológico. Veinticuatro por ciento de todos los tumores fueron astrocitomas, 20% meduloblastomas y 11% ependimomas. Los gliomas constituyeron el 84% de todos los tumores en las series. Los tumores fueron encontrados en seis infantes de un año o menores; dos en infantes de dos meses. Los meduloblastomas y los ependimomas fueron más comunes en niños menores de seis años. Sesenta y seis de todos los tumores fueron infratentoriales.

Bajo las condiciones actuales en la Clínica Mayo, 54% de todos los niños que se operan por tumor en el cerebro viven seis meses o más. De 356 pacientes que se observaron por cinco años o más después de la operación, 13.3% vivieron por lo menos 5 años. El período de vida más largo ha sido 20 años después de haberse removido un astrocitoma, y este paciente todavía tiene esperanza de vivir más tiempo.

Mayo Clinic

PHONOCARDIOGRAPHIC DIFFERENTIATION OF THE MURMUR OF MITRAL INSUFFICIENCY FROM SOME COMMONLY HEARD ADVENTITIOUS SOUNDS IN CHILDHOOD

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SINCE cardiac murmurs are relatively more important for the diagnosis of heart disease in children than in adults, it is unfortunate that adventitious sounds not significant of heart disease are found so commonly in children. The interpretation of murmurs heard over the child's heart involves a differentiation between those which occur normally and those which imply pathologic change.

Of the nonpathologic systolic murmurs which must be differentiated from that of mitral insufficiency, some are distinguished on the basis of location or point of maximum intensity; others, largely on the basis of acoustic quality.[1] The former involve primarily those pulmonic systolic murmurs and other parasternal systolic murmurs which are loud enough to be transmitted well toward the apex. These may give rise to a false diagnosis of mitral insufficiency if auscultation is carried out only over the apex of the heart. A reasonable amount of care in exploring the precordium in such cases will show that the same murmur which is heard over the apex becomes progressively louder as one ranges toward the sternum, and will thus indicate the nonmitral origin of the murmur.

The other group of innocent murmurs are those which must be differentiated primarily by their acoustic quality from the murmur of mitral insufficiency. By far the greatest number of these innocent murmurs fall into the category of the precordial murmur described by Still[2] as a "twanging-string" murmur because its quality is reminiscent of the vibrations of a plucked string. The importance of recognizing this murmur in order to avoid false diagnoses of rheumatic heart disease has been given the great emphasis it deserves by Ash.[3,4] At its lowest intensity this murmur may simply give the impression of prolonging the apical first heart sound; at its loudest, it presents a clear musical tone, almost buzzing in quality. The distinction between this murmur and that of mitral insufficiency is made largely on the basis of acoustic quality, primarily on the absence of any blowing quality in the former. In many cases, the differentiation is facilitated by the fact that the maximal intensity of the "twanging-string" murmur is usually to the right of the apex of the heart. Since the location, or the point of maximal intensity of the murmur, is frequently within a centimeter or so to the right of the apex, the physician cannot depend on difference of location of the point of maximum intensity to distinguish this murmur from that of mitral insufficiency. This distinction must, then, depend largely on acoustic quality rather than location or relative intensity and is, therefore, the more difficult and requires more experience. Since this innocent murmur is, moreover, common in child-

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hood,[5] it presents by far the most important differential problem in the diagnosis of rheumatic heart disease in both the apparently healthy and the acutely ill child. For this reason a comparative analytic study by phonocardiography was instituted of the characteristics of the apical systolic murmur of mitral insufficiency, the normally occurring "twanging-string" murmur, and a few others.

Phonocardiography, or stethography, consists of the visual or graphic recording of the wave forms of the heart sounds as heard through the stethoscope. As long ago as 1933, Bass et al.[6] adapted an especially constructed instrument to this problem. More recently, there have been several independent developments of instruments to record cardiac murmurs in this manner,[7-9] and several studies of adventitious heart sounds by such apparatus.[10-22]

Methods and Materials

The patients examined were seen largely in the Rheumatic Fever Clinic of The Philadelphia General Hospital, which functions in part as a diagnostic clinic and, therefore, admits many children with miscellaneous undiagnosed cardiac murmurs. Other children were studied in the wards of the 2 hospitals from which this work is reported. Each child was examined by auscultation by the 3 authors, and a written description of the murmur was made, separately, by each. Phonocardiographic tracings were then made over the point of maximum intensity of the murmur and at any other location on the precordium indicated by the physical examination. The children were in every case thoroughly studied by the routine examinations of the clinic, which are in part directed at substantiating or refuting a diagnosis of congenital or rheumatic heart disease. All children referred to the clinic in whom any murmur is heard are followed at intervals of several months for a considerable period, and the children with the murmurs not of blowing quality included in this study had been studied clinically on many visits over periods up to 4½ yrs. without any indication of heart disease. The patients referred to below as having mitral insufficiency had, in all cases, an unequivocal diagnosis of rheumatic heart disease and a typical apical systolic murmur of blowing quality transmitted at least to the anterior axillary line. The murmurs of mitral insufficiency recorded and analyzed in this study covered a considerable range of intensity. Extremely faint and extremely loud murmurs of this character were not included.

The apparatus used for the graphic recording of heart sounds was the Sanborn Stethocardiette, the structure of which has been described by Rappaport and Sprague.[9] This instrument is similar to the "Stethograph" described some years before.[7] In this instrument vibrations derived from sounds are recorded as waves which appear as a graphic representation of the sounds "picked up" by a stethoscope. Of the several stethoscope attachments available, the medium bell was employed in this study. Some recordings were repeated with the logarithmic microphone; these showed the same effects which will be indicated below.

Results

Phonocardiographic tracings were recorded in 15 children with mitral insufficiency due to rheumatic heart disease, 30 children with nonblowing systolic apical or precordial murmurs, and a number of children in whom no cardiac murmur was heard. Figure 1 illustrates three heart sound tracings taken from patients in whom no cardiac murmur was audible. Of the 30 nonblowing murmurs, 25 were typical "twanging-string" murmurs, varying over a considerable range of intensity. The loudest of these presented a certain element of buzzing quality.

Examination of the tracings revealed a definite difference between the murmurs of valvular insufficiency and the "twanging-string" murmurs. The most striking difference was in the pattern of the tracing (Fig. 2).

Examination of the sound tracing in Fig. 2 shows that those obtained from children

with "twanging-string" murmurs have a uniform wave form of constant frequency, such as is classically produced by a single pure tone without overtones. The frequency of this tone is easily measurable. The lower two tracings of Fig. 2 are typical of those recorded in cases of valvular insufficiency. They are seen to be entirely different in that there is no uniformity of frequency or amplitude and no definite pattern. The five remaining nonblowing murmurs were not "twanging-string" murmurs but exhibited other non-

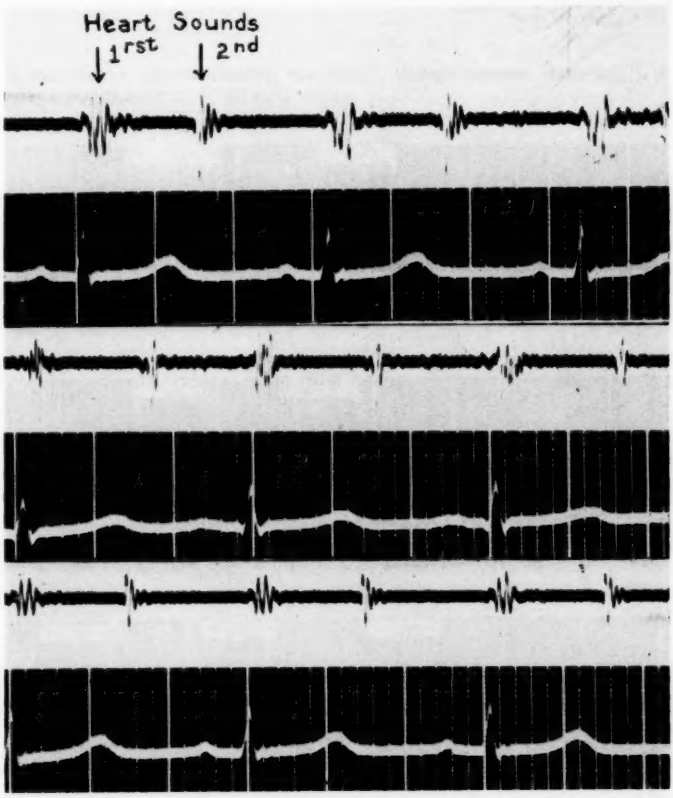

FIG. 1. Heart sound tracings in children in whom no murmur was audible.

blowing acoustic qualities. Two of these had a definite grating quality. Two were best described as snorting, and one had a scraping character. The phonocardiographic tracings of these murmurs also showed a single uniform wave, so similar to the tracings produced by the "twanging-string" murmurs as to be indistinguishable from that group. Since all of the nonblowing precordial or apical murmurs presented tracings of the same kind, regardless of their acoustic quality, they were grouped together for purposes of analysis and comparison with the murmurs of mitral insufficiency.

Analysis of the 45 tracings showed some points of similarity and some differences between the murmurs of valvular insufficiency and the nonblowing murmurs. A comparison of the time-relations of the murmurs in the interval between the first and second sounds

showed that the murmurs of insufficiency began immediately after the first sound, with no silent interval, and that they extended throughout systole. They were of constant intensity throughout systole or of maximal intensity during the middle third of this period. The vibrations of nonblowing murmurs, on the other hand, were always sepa-

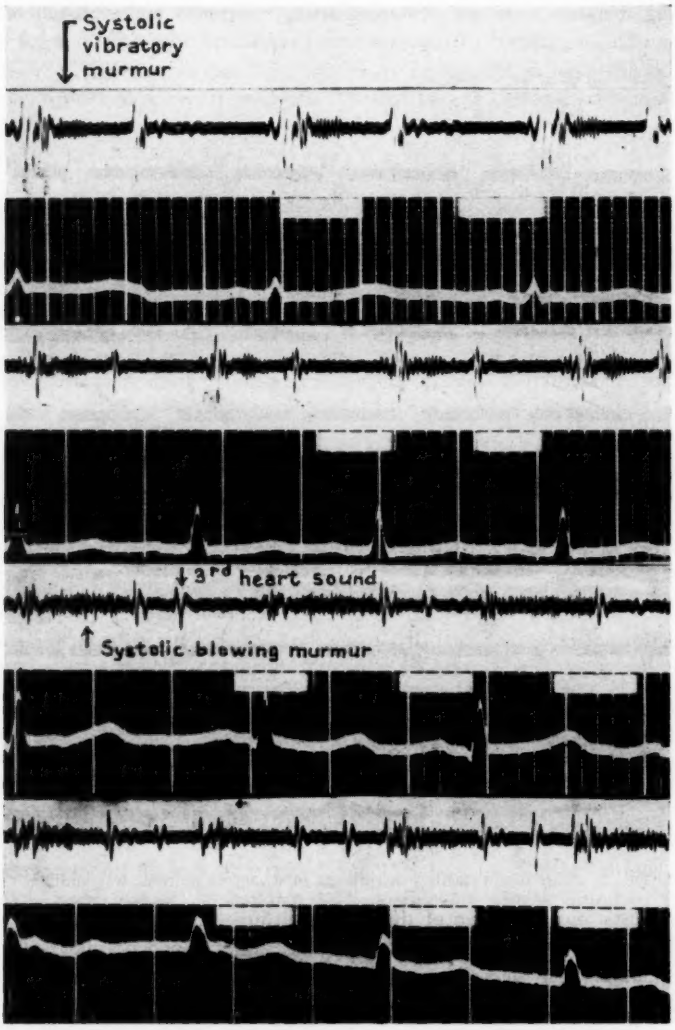

FIG. 2. Typical sound tracings of vibratory murmurs (upper two) and of murmurs of mitral insufficiency (lower two).

rated from the first heart sound by a brief interval, were almost entirely confined to the first and second thirds of the period of systole, and usually had a defined maximum of intensity in the middle third of this interval.

TABLE I

SOME PHYSICAL CHARACTERISTICS OF SOUND TRACINGS OF TWO GROUPS OF SYSTOLIC MURMURS

	Duration of Murmur			Intensity of Murmur		
	Mean in seconds	Standard error of mean	Mean fraction of total length of systole	Mean in mm. of amplitude on tracing	Standard error of mean	Mean fraction of intensity of first heart sound
Murmurs of mitral insufficiency	0.24	0.006	0.786	5.4	0.5	0.43
Nonblowing murmurs	0.114	0.003	0.326	5.9	0.4	0.46

Comparisons of the two groups of murmurs were also made with regard to duration and intensity. The duration of the murmurs of mitral insufficiency was on the average of 0.24 sec., which was significantly greater than the 0.114 sec. average of the nonblowing murmurs. Since the interval corresponding to systole was somewhat shorter in the hearts with rheumatic heart disease than in the presumably normal hearts, the relative length of systole occupied by murmurs of mitral insufficiency was, again, significantly greater than in the case of the nonblowing murmurs.

Comparison of the intensities of the two groups of murmurs, however, showed no such difference. The average amplitude of the "twanging-string" group was somewhat greater

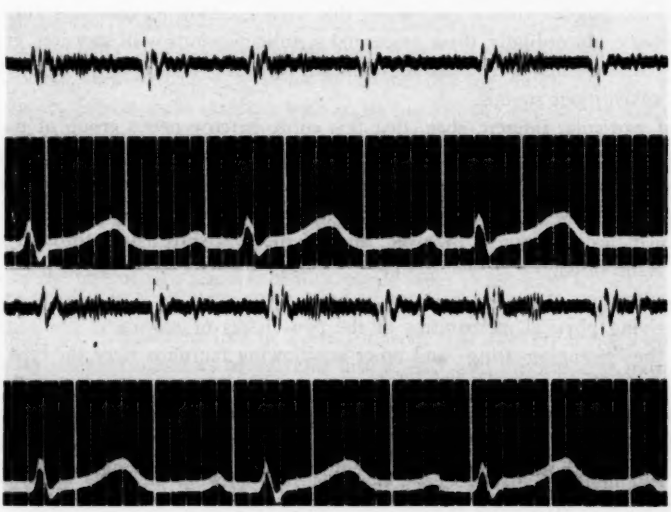

FIG. 3. Heart sound tracings in children with "mixed" vibratory and blowing systolic murmurs. Tracings of individual systolic murmurs are seen to contain portions typical of "twanging-string" vibrations and other parts typical of the murmurs found in mitral insufficiency.

than that of the murmurs of valvular insufficiency, although this difference is not statistically significant. There was no difference, again, between the intensities of the two murmurs in relation to the intensity of the respective preceding heart sound, since the mean amplitude of the first heart sound was similar in the two groups. Table I summarizes these similarities and differences.

In a few of the children with rheumatic fever, a clinical impression of a mixed murmur was made. In these children there was a murmur of moderate intensity, usually confined to the apex, with only a slightly blowing character, so that it was assumed on clinical grounds that a slight degree of mitral insufficiency was superimposed on a pre-existing "twanging-string" murmur. In the tracings obtained from these children, waves corresponding to the systolic murmur were of a mixed character, including some rather uniform waves set in a group of the irregular ones characteristic of blowing murmurs. Such tracings are shown in Fig. 3.

Discussion

Throughout this paper the implication has been made that all of the murmurs which were not blowing in quality were not associated with disease. In the case of the "twanging-string" murmurs, such an assumption could be made without clinical data on the subjects involved in the study, inasmuch as this murmur has been associated with the normal hearts of children, especially by the work of Ash.[3, 4] As a matter of fact, however, these children were all under specialized study in this clinic, and in all cases repeated examinations had failed to demonstrate any substantial change in the nature of the murmur or any other evidence of heart disease. In the five remaining children of the group with nonblowing murmurs, this was also true. The latter, because of the bizarre type of murmur, were seen more often in the clinic and studied with special care, as were those with the loudest "twanging-string" murmurs. Study over periods up to 4½ years, however, confirmed the original clinical impression that these nonblowing murmurs did not imply cardiac disease. Accordingly, these precordial systolic murmurs with snorting, grating and scraping characteristics, were classified clinically with the "twanging-string" murmurs as innocent adventitious sounds.

It is of particular interest, then, that this entire heterogeneous group of nonblowing murmurs produced the same regular wave pattern in the phonocardiograph, regardless of the acoustic effect. It seems probable that the same physical mechanism is responsible for all, and that the volume of the murmur and its acoustic quality may depend on precisely which cardiac tissue is involved, and on the overlying tissues through which the sound is transmitted.

An examination of the wave forms in heart sound tracings is of interest in terms of the underlying physical mechanisms of the two classes of murmurs. The regular wave form of the "twanging-string" and other nonblowing murmurs is of the type produced by an object vibrating at its natural frequency without overtones. Since a tuning fork produces just this sort of sound or vibration, phonocardiographic tracings were made of a vibrating tuning fork of frequency 128/sec., and these were, in fact, similar in regularity of form to those produced by the entire group of nonblowing murmurs. It would seem probable that in the juvenile heart some part of the relatively soft tissue may, under some circumstances, be set into a brief natural vibration by the systolic flow of blood and, if the physical factors involved cause this vibration to be of audible intensity, a "twanging-string" murmur results. The acoustic difference between "twanging-string" murmur

and the comparatively rare group of the snorting and grating systolic sounds may involve a difference in the geometric form or relations of the vibrating tissue. In terms of this theory, the relative rarity of such murmurs in adults would be ascribed to the firmer character of the tissue in the adult heart, so that the velocity and pressure of flow in systole would fail to produce so great an effect.

The tracings yielded by the murmurs of mitral insufficiency were also studied. Wave forms other than the uniform ones given by the "twanging-string" murmurs might be produced in the following ways: by a simple vibration of such high frequency that the inertia of the recording instrument does not permit a faithful recording of it; by a fundamental tone and overtones whose combined effect involves vibrations too fine or frequent for the recording instrument; or simply by a disorganized mixture of unrelated frequency, like that produced by a jet of steam or fluid. Two of these possibilities were tested in an attempt to explain the wave form produced by the murmurs of mitral insufficiency. First, vibrations of tuning forks of higher frequency were recorded by the phonocardiograph. It was found that the instrument had little enough inertia to record vibrations of a frequency over 500/sec. Since the fundamental frequency, if any, of the murmur of mitral insufficiency is certainly not as high as 500/sec., mere pitch cannot account for the irregular wave form corresponding to that murmur. Second, tones with fundamental frequencies similar to that of "twanging-string" murmurs were played on musical instruments and recorded on the same apparatus. A pattern was produced which, while it was not of the simple sine-curve type produced by "twanging-string" murmurs or tuning forks, was definite and regular and was repeated in cycles, in contrast to the complete irregularity found in tracings of murmurs of mitral insufficiency. Since the evidence indicates that neither a high-pitched tone nor a lower tone with overtones gave rise to the irregular wave form found in the murmur of mitral insufficiency, it is concluded that this pattern represented a mixture of vibrations of unrelated frequencies. The fact that such vibrations are produced by jets of steam and fluid makes it seem probable that this wave form represents the vibrations derived from the actual regurgitation of fluid through the incompetent valve or orifice. In order to confirm this suggestion, tracings were taken over the appropriate areas in children with aortic insufficiency and interventricular septal defects. The same type of wave pattern was found as in the tracing of mitral insufficiency.

Clinically, these data lend additional weight to the importance of the quality of a murmur in the child's heart, inasmuch as they would suggest that the murmur of blowing character represents the actual flow of blood under abnormal conditions. On the other hand, apical or precordial systolic murmurs, which are distinguished from blowing murmurs by the lack of that acoustic quality, would seem to represent some type of vibration of cardiac tissue and thus have quite a different clinical significance.

Conversely, the data summarized in Table I indicate that intensity is not a differentiating character between murmurs of valvular insufficiency and the innocent murmurs. No significant difference was found by phonocardiography between the intensity of these two types of murmurs, and although some of the nonpathologic murmurs were of maximum intensity at the mid-precordium, many were recorded at the apex or near that point. The intensity of these nonblowing murmurs was not essentially different from that of others in the group. This finding bears out our clinical impression that classifications of the pathologic significance of apical murmurs by their intensity, as advocated by Levine,[23,24] do not apply to the differential diagnosis of rheumatic heart disease in children.

A note on terminology. Throughout this paper the term "twanging-string" murmur has been used to denote the vibratory nonblowing murmur heard over the precordium of many children without cardiac disease. This has been done in conformity with the usage of Still and of Ash. Tracings which we have taken in the course of these studies indicate that vibrations of such low frequency, without overtones, as are given by this murmur, are not produced by vibrations of strings, whether they are relatively thick or thin, at high or low tension, of musical instruments or ordinary packing cord. On the other hand, vibrations of solid structures, such as a tuning fork, have been found to have a wave pattern similar to that of the normal murmur under discussion. It would therefore appear to be advisable to use, rather than "twanging-string murmur" or "twanging murmur," the term "vibratory murmur," for this normally-occurring murmur, in contrast to the "blowing murmur" of valvular regurgitation. The term "vibratory" is not only more descriptive of the physical facts than is "twanging," but has an incidental pedagogic advantage in that the term "twanging" often conveys a false impression of a nasal or egophonic character of this murmur to physicians not familiar with it.

Summary

Phonocardiographic tracings were recorded in children with known insufficiency of the mitral valve, children with a variety of systolic murmurs without blowing quality and children with no audible cardiac murmurs.

The murmurs of valvular insufficiency produced tracings with a completely patternless and disorganized wave form. The other nonblowing murmurs all yielded tracings of uniform sine-wave character, regardless of their acoustic quality. Of these, the majority were "twanging-string" murmurs, the loudest of these with a distinct buzzing quality; the others were "snorting," "scraping" or "grating" in quality. Clinical observations indicated that these nonblowing murmurs were not indicative of cardiac disease.

The murmurs of mitral insufficiency were significantly longer than the nonpathologic murmurs, but the latter showed, on the average, fully as great amplitude on the tracings.

Physical and clinical implications of these findings are discussed.

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SPANISH ABSTRACT

Diferenciación Fonocardiográfica de los Murmullos de Insuficiencia Mitral de algunos Sonidos Adventicios comunmente oídos en la Niñez

Este estudio presenta una comparación, por fonocardiografía, del murmullo sistólico apical de insuficiencia mitral y algunos murmullos funcionales con un vibratorio peculiar o clase de zumbido que comunmente se oye en la niñez. Estas señas obtenidas de niños con murmullos vibratorios inocentes tenían una forma de onda uniforme de frecuencia constante, tal como producida clásicamente por un solo tono sin armónicos. La frecuencia de este tono se puede medir facilmente. Las señas típicas de insuficiencia valvular son enteramente diferentes. En éstas no hay uniformidad de frecuencia de amplitud y no hay patrón definible. Las fotografías de las huellas demuestran que estas características están presentes. Se tratan algunas complicaciones físicas de estos descubrimientos.

También se hizo un análisis de la duración, intensidad y situación en el ciclo cardiaco de los dos tipos de murmullos. Este demonstró algunas diferencias constantes y significativas. Los murmullos de insuficiencia mitral fueron significativamente más largos que los murmullos no patológicos, pero los últimos mostraron, por lo regular, gran amplitud.

Clinicamente, estos informes prestan respaldo adicional a la importancia de la clase de un murmullo en el corazón del niño. A la inversa, ellos demuestran que la intensidad no es siempre un criterio de diferenciación válido entre murmullos de insuficiencia valvular y los murmullos inocentes.

Se ofrece una explicación a base física por el carácter vibratorio de ciertos murmullos funcionales en la niñez.

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SPECIAL FEATURE SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

EDWARDS A. PARK, M.D., *Editor,* PAUL HARPER, M.D., *Associate*

Statements appearing in this column do not necessarily reflect the opinion of the editors nor are they to be interpreted as the official opinion of the Academy.

INTRODUCTION

DR. W. MONTAGUE COBB, who prepared the article which follows, is the professor of anatomy at Howard University School of Medicine, Washington, D.C., and is recognized as one of the foremost Negro educators in this country. He is chairman of the Council on Medical Education and Hospitals of the National Medical Association and a member of the National Medical Committee of the National Association for the Advancement of Colored People. His article describes the difficulties and obstacles encountered by Negroes in this country in obtaining medical education and shows the paucity of Negro physicians and the dearth of facilities for medical care of our 14,000,000 Negro people.

It is generally admitted that the greatest difficulty in our current medical care structure is the appalling lack of personnel and facilities for the care of the Negro. The Negro and white races are so intermingled in their working and living arrangements that the health of one race is profoundly influenced by the state of health of the other. Sickness in the Negro undoubtedly takes its toll among the white race. But the real reason why good medical education and good medical care should be provided for the Negro race is not this, but because they need it for their own happiness and welfare; as citizens of this country they are entitled to equal opportunity to obtain good medical care.

If the editors of the column may be permitted to express their own personal views, it is that qualified Negroes should be admitted to our medical schools and should subsequently be given the necessary opportunities to obtain working experience in our hospitals and clinics.

BROWN AMERICA'S MEDICAL DIASPORA: A PARADOX OF DEMOCRACY

By W. MONTAGUE COBB, M.D.

OUR BROWN TENTH

FOLLOWING the Babylonian captivity, the colonies of Jews dispersed about the ancient world became collectively known as the Diaspora. In these nuclei the spirit and culture of a great people struggled against terrific odds to keep alive and progress. Today in our own United States there are spread over the land varieties of health facilities which form a kind of medical Diaspora, brought into being and maintained by attitudes toward ethnic group instead of religion.

The group constitutes one tenth of our population, some 15 million people, who carry in varying proportions genes from all three major human stocks, Negroid, Caucasoid and Mongoloid. They have been termed a new race, the "Brown American." They know no homeland but the U.S.A. and no political ideal but democracy. They have sealed this allegiance with blood freely shed in all our country's wars and they desire no rights or privileges beyond those guaranteed all citizens by the Constitution.

RETARDED HEALTH IMPROVEMENT

Through segregative devices of varying kind and degree, our brown Americans have been denied equality of opportunity in our national life. The ill effects of this inequity are nowhere more dramatically illustrated than in the field of health, where progress in medicine, public health and general welfare has increased the average life expectation of an American from 35.5 years in 1789 to about 64 years today. Yet, over the period of the record, Negro life expectancy has shown a constant lag of about a decade behind the white. In 1940 the life expectation of Negroes at birth was 52.26 years for males and 55.56 years for females; that of whites 62.81 years for males and 67.29 years for females.[1]

The Negro mortality rate has declined from 24.1 in 1910 to 14.0 in 1940, but the latter figure was 71% higher than the rate of 8.2 for whites. So that although the Negro has shared in the benefits of modern medical advances, he has never done so as fully or rapidly as the rest of the population and he brings up the rear of backward regions.

Moreover, nearly all diseases which show excess mortality in the Negro are classed as preventable. Such conditions as tuberculosis, maternal and infant mortality, and venereal disease regularly show high rate in any group of low economic status, where there are ignorance, overcrowding, poor nutrition, bad sanitation and lack of medical care.

THE NATION'S RESPONSIBILITY

As disease knows no color-line, poor health conditions, wherever found, constitute a national problem. In his recent report to the President,[2] the Federal Security Administrator stated that every year in the United States 325,000 people die whom we have the knowledge and skills to save; that every year we lose 4,300,000 man years of work through bad health; and that every year the cost of sickness and partial and total disability in national wealth is 27 billion dollars.

The Administrator states forthrightly that, "It is the Nation's responsibility, and to the Nation's advantage, to do its utmost to insure that all people everywhere attain the highest possible level of health."[3] He says further that:[4]

The relative lack of Negro physicians must be given special attention. Negroes comprise 10% of the total population but produce only 2% of the country's physicians.

We can no longer tolerate in our society a system of medical care under which Negro physicians and Negro patients are discriminated against.

There should be no racial barriers in the provision of adequate medical care. Qualified Negroes must be admitted without discrimination to the health professions, and to the use of training and health facilities. Their general educational opportunities also must be improved greatly so that more Negroes can qualify for the professions. The opportunity to study and practice medicine should be open to all eligible candidates regardless of race, creed, or sex.

So positive a pronouncement from so responsible a source warrants the fullest possible exposition of the facts which evoked it. It is hoped the following brief survey will be a contribution to that end.

Discriminatory Patterns

Discriminative practice in medicine victimizes more than one minority and is not confined to any particular region. Negro, Mexican, Filipino, Japanese, Chinese, Italian and Jew, all know the effects of these practices. The Negro is the largest group affected and against him the patterns have their fullest and most extreme expression.

South, North, East and West all have their discriminatory practices, sometimes frankly, sometimes subtly executed. Discrimination is at its worst in the South where the bulk of the Negro population is concentrated.

The practices are manifest in respect to hospitals, medical education and medical organizations. They apply to patient, physician, student, teacher and consumer of medical service plans.

Hospitals.—In many places, in the South especially, no hospital facilities whatever are available to Negroes. Over much of the South the colored "basement ward" is notorious where no attempt at an acceptable hospital set-up is made. Negro patients are admitted for what attention the white physicians will give them, often with a single untrained attendant as nursing staff.

One may see white institutions which admit Negro patients long enough to permit them to be operated upon, but while still under anaesthesia or a few hours afterward, shunt them over to a nearby Negro institution without staff, equipment or technical knowledge to supply modern postoperative care.

In tax-supported hospitals Negro patients are generally accommodated. This admission is regularly on segregated wards or to separate institutions in the South and not infrequently elsewhere. The quality of the segregated accommodation is usually inferior. In Chicago, the home of the American Medical Association, Negroes constitute a majority of the patients who pay to enter the public Cook County Hospital, a curious reflection of the unavailability to them of hospitalization elsewhere.

Voluntary hospitals on a country-wide basis are the greatest offenders as to exclusion practices. Even the Federal veterans' hospitals are guilty, for of 127 such hospitals operating as of November 3, 1947, 24 had separate wards for Negro veterans and 19 of the hospitals, all located in the South, did not admit Negroes at all except in cases of medical emergency.

Appointments to either resident or visiting staffs have been available to Negro physicians in only about a dozen hospitals in the entire country, excepting Negro institutions. The attempt to compensate for those barriers has led the Negro to develop his own institutions as described below.

Medical Education.—There are 79 approved medical, 36 dental and 65 pharmaceutical schools in the country. These collectively constitute a national resource for the training of health personnel, in the same sense that our military academies are a national resource for the training of officers for the Armed Forces. In recognition of their essential public service, many of our medical educational institutions are tax-supported and all are tax exempt. For the same reasons they should be freely open to all qualified students. Yet, until recent months, 26 or an approximate third of the medical schools, 16 or nearly half of the dental, and 20 or about a third of the pharmaceutical schools did not admit Negro students. Paradoxically, the large majority of these excluding institutions are in the South where the largest Negro population and need for health services are located.

Of the schools in the North and West admitting Negro students, some only occasionally have had such students on their rolls. Many have expressed a willingness to admit more if they could get better qualified applicants. Rising standards and increased competition for the limited professional school openings have not favored the Negro student, who, on the whole, has not enjoyed the best pre-professional preparation.

For health personnel again, the Negro has had to depend mainly upon Negro institutions.

Medical Organizations.—With one exception, south of the Mason-Dixon line the Negro is excluded from membership in the official county and state medical societies recognized by the American Medical Association and hence from membership in that association and from staff appointments to most approved hospitals.

Here also he has been forced to form his own parallel organizations of greater or less significance. So throughout the South and in most large northern cities there are local colored medical societies. There are state organizations in the South and in some northern states, the National Medical Association formed in 1895 representing the whole.

In those areas where the Negro physician is eligible for membership in his county society, he frequently sees a need for the local colored society and the National Medical Association, and he is regularly urged to join both, so as to support his less advantaged brethren. When he does so, the price of segregation is two sets of medical organizational dues.

The advent of the various types of prepayment medical care plans has witnessed new discrimination against the Negro both as patient and physician. As patient he may be excluded altogether. Sometimes he may be admitted, but as in a certain major city where Negroes may join the Blue Cross, the only facility available is a decidedly inferior separate hospital. In county medical society plans, where Negro physicians cannot join the societies, they may be allowed to treat patients under the plan, but have no voting privileges.

Ghetto and Diaspora

A major product of these discriminatory patterns, which have obtained since the Civil War, has been what the writer has termed the Negro "medical ghetto,"[5] meaning the sum of what the Negro, often with white support, has been able to develop as separate

medical educational and hospital facilities. There have been eight Negro medical schools of which the first two established above survive.

These two institutions, the Howard University School of Medicine in Washington, D.C., and the Meharry Medical College in Nashville, Tenn., which from their inception have trained the large majority of Negro physicians (about 85%), form the heart of our "medical ghetto." The primary field centers are about 10 Negro hospitals and about 10 additional hospitals in the North and West, where most Howard and Meharry graduates serve their interneships and obtain advanced training in residencies and specialties. These few institutions determine to a large extent the type and quality of medical service the public can receive from Negro health personnel. About 112 Negro hospitals of varying grade about the country, proprietary, voluntary or supported in part by public funds, constitute secondary units in the ghetto system, providing as they do the only institutions in which the majority of Negro physicians can work, if they do hospital work at all. Fuller historical and descriptive treatment of the Negro medical institutions appears elsewhere.[5,6]

The Negro physician, and to an increasing extent the Negro public, have become aware of the ghetto-like nature of these arrangements and they have made of them a diaspora, the units of which intercommunicate through the mails, personal visits, exchange of staff, clinical symposia and periodic organizational meetings, the Negro weekly press and in less formal ways. Day by day the national Negro community keeps informed on developments respecting the common problem of discrimination in medicine and plans and adjusts its own moves concerning them. Sometimes attitude and action are logical and effective. Often response is tardy, loosely organized and ineffective, but the bass note is always the same, resentment against the futility, inadequacy and impracticability of the segregative plan and clear perception that only through its total abolition can equity in health care for all Americans be achieved.

The brown medical diaspora is often torn with schisms, generally on an area basis concerning the approach and methods of attack upon the common problem. Sometimes the differences between groups absorb energy that should be devoted to the basic difficulties, but this has been rather universal in human experience.

Deficits, Needs and Fears

There are today about 3,900 Negro physicians, 1,600 dentists, 9,000 nurses and 1,400 pharmacists. The accepted minimal standard of safety is 1 physician to 1,500 of population. The national average is about 1 to 750. In 1942, the proportion of Negro physicians to Negro population was 1 to 3,177. The range by states was from 1 to 1,002 in Missouri to 1 to 18,527 in Mississippi. But two cities in the country, Washington, D.C., and St. Louis, Mo., approximated the national average of 1 to 750.[7]

It is not our premise that the number of Negro physicians in the United States should be determined by the number of Negroes in the population, but considering physician-population ratio on a racial basis, there should be 9,334 colored physicians today, assuming a Negro population of 14,000,000. This is more than twice the existing number. Consequently, a large portion of the Negro population receives such medical care as it obtains, from white physicians, who, in many cases, find this service an inconvenience.

In 1947 the combined enrollment of the Howard and Meharry medical schools, plus 82 colored students in 20 northern and western schools made a total of 590 Negro doctors in training. There were then approximately 25,000 medical students in the country.

If Negro students were enrolled according to population percentage, there would have been 2,500.

About 135 Negro doctors are graduated annually. Howard and Meharry produce about 60 each and a dozen or so are graduated from northern and western schools. Howard and Meharry have both been operating at or above capacity for some time. In their entire history, there have only been two years, 1944 and 1946, when the combined output of both schools has been as high as 125 physicians. In 77 classes, 1871 through 1947, Howard has graduated a total of 2,277 physicians, and Meharry in 72 classes, 1877 through 1947, a total of 2,983 physicians, a combined production of 5,260.

Howard has graduated a total of 1,075 dentists, 1885 through 1948, and Meharry a total of 1,220, over the same period, both together having produced 2,306 dentists. The two schools now graduate a combined total of between 65 and 70 dentists annually.

In both medicine and dentistry the prevailing annual number of graduates is scarcely the number necessary for replacements for deaths and retirements. It cannot keep pace with the growth even of the Negro population, much less contribute to the general need for increased health personnel described in the Federal Security Administrator's report to the President.

A new Negro medical school is not to be considered not only because of the practical problems of staffing and financing, but because the paradox of a segregated institution in a free democracy is no longer tolerable. All effort should be in the direction of eliminating segregation rather than extending it.

The production of larger numbers of properly qualified professional school applicants is a vital essential. Adequate preparation in many of the jim-crow educational systems where most Negro pre-professional students are trained is impossible of achievement. Most of the states which have separate systems can hardly afford one good educational system, much less try to maintain two. The need for improvement in preparation goes back to the kindergarten. Reasonable opportunity for neither whites nor Negroes can be afforded in poor states with dual systems, but where the white facilities are bad, those for the Negro are always much worse.

Rising standards have created a demand for more certified specialists. In many categories where new openings for Negro physicians have appeared, it has not been possible to find personnel to fill them. This has been particularly true of medical specialists. Since the first Negro specialist became certified in 1927 there have been 111 Negro diplomates of specialty boards of whom 106 are living and one has been certified by two boards. They are distributed as follows: internal medicine—11; surgery—19; otolaryngology—9; psychiatry and neurology—9; dermatology—6; obstetrics and gynecology—9; urology—4; pediatrics—15; radiology—16; ophthalmology—10; pathology—3.

As none, second, third or fourth rate hospitals have largely been the portion of our Negro citizens, lack of adequate hospital facilities has been the greatest material handicap to the receipt of adequate medical care by the patient and adequate postgraduate training by the profession.

Of the 120 Negro hospitals in the United States, some 25 are accredited and 14 approved for training of internes and residents. The number of hospital beds currently available to Negroes is in the neighborhood of 10,000. The currently accepted standard requires 4.5 general hospital beds per 1,000 of population. In "some areas where the population is heavily Negro there are as few as 75 beds set aside for over one million of this group."[8]

The spirit behind the Hospital Survey and Construction Act (Public Law 725—79th Congress) to give aid to states in the construction of needed new hospitals, clearly aims to make beds available where they are needed irrespective of race, but the provisions for implementation provide loopholes around the anti-discrimination clauses.[6] The extension and perpetuation of segregation through new hospital construction is particularly to be guarded against, as it is being attempted in the North as well as the South.

In this vital period in our history when forces which would bring our democratic preachment into more practical realization come into conflict with those which would maintain the *status quo* at any cost, we find minorities beset with some confusion and many fears.

In a certain major eastern city, for example, a Negro hospital with a long and honorable tradition is in financial straits. All concede that it is no longer essential as its patient load could be easily absorbed elsewhere. The Negro profession, however, is suspicious of representations that those qualified among them may obtain appointments on other hospital staffs. They are fearful that if they release the little they have they will find themselves with nothing and they want the new appointments to come first and be proved bona fide before they sign away a meager birthright.

All over the country the Negro physician and interested public finds itself in the valley of decision on a variety of relatively small matters of highly significant implications. It is a time for insistence on principle lest we damn posterity.

Recent Developments

Shortly preceding and now paced by the President's Civil Rights Program, there have been a number of indications that the predicament of the Negro in health facilities was afflicting the national conscience and that remedial measures were being seriously entered upon.

The President's Commission on Higher Education and the Commission on Hospital Care sponsored by the American Hospital Association each recommended the abolition of segregative practices in their respective spheres. The American Nurses Association has legislated to admit to membership qualified Negro nurses who cannot become members of their local county or state societies.

The Gallinger Municipal Hospital in Washington, D.C., through tactful effort by the Federal Security Administrator Oscar R. Ewing, has opened to the professional staff and student body of the Howard Medical School. About the land several other hospitals, public and voluntary, have appointed Negroes to staff positions. The Federal Security Agency is making extensive study of the problems of premedical preparations.

The American College of Surgeons has completely relinquished its racial exclusion policies and at last count had admitted to fellowship 20 Negro surgeons. The other professional "colleges" appear to be admitting Negro fellows as they qualify.

A southern medical association, the Baltimore City Medical Society, an official American Medical Association affiliate, voted in December 1948 to admit Negro physicians to membership.

A southern medical school, that of the University of Arkansas, last fall admitted a Negro student without differential provisions. Georgetown University in Washington, D.C., has admitted a Negro medical student, Jefferson Medical College in Philadelphia which allegedly has not had a Negro student in 30 years has admitted one. The medical school of the University of Chicago, which was picketed last year because of its apparent

policy of no longer admitting Negro students, has accepted one. The faculty of Washington University Medical School in St. Louis has voted to admit Negro students and its sister school at St. Louis University has indicated a willingness to accept them. The University of West Virginia, in the light of the Gaines and Sipuel Supreme Court decisions, has admitted Negroes to its graduate school without mishap and now contemplates their acceptance in the medical school as well. A number of northern and western medical and dental schools which have always had occasional Negro students have manifested a willingness to take more as such students qualify according to their standards.

The adoption of the regional education program by the Southern Governors Conference on December 13, 1948, at Savannah, Ga., may temporarily set back the clock a bit. An immediate application of the plan was approval of a $600,000 biennial fund for the support of Meharry Medical College. Southern schools which had opened their doors or contemplated doing so may now shunt Negroes of the locales to Meharry. If this develops, the National Association for the Advancement of Colored People has pledged itself to fight the plan to the Supreme Court as a device for the perpetuation of segregation.

It should be only too apparent to all concerned, however, that what the nation needs are 79 or more medical schools open to any qualified students and not the present incongruous arrangement whereby two schools are supposed to furnish the bulk of Negro health personnel with a minor helping hand from northern and western schools, while nearly a third of our schools located in the heart of the Negro population bar professional students of that extraction.

The pendulum has begun to swing in a corrective direction. It is up to all interested in making American practice equivalent to American preachment to keep it so swinging.

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TRENDS

IN HEALTH LEGISLATION AND ADMINISTRATION

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

SCHOOL HEALTH SERVICES BILL (S.1411)

IN THIS column in April, we reported that a new School Health Services Bill was being drafted in the Health Sub-Committee of the Senate Committee on Labor and Public Welfare. On March 25, this Bill came out of Committee and was introduced into the Senate by Senator Thomas (Democrat, Utah) as S. 1411. Sponsoring this Bill with Senator Thomas was the entire membership of the Health Sub-Committee, with the addition of Senator Saltonstall, who introduced the School Health Service Bill (S. 1290) a year ago in the Eightieth Congress.

In the opinion of several of those who are close to the Washington scene, this School Health Services Bill is one of the health measures most apt to meet with favorable and early action in the current session of Congress. While the battle rages over a comprehensive health program, a health measure which is less contentious may be enacted. Following all the electioneering promises it would be surprising if this session of Congress were to close without some health legislation which can be held up as accomplishment. S. 1411 is scheduled for early action in the Senate; in the House there have been several additions to the roster of the sponsors of School Health Services legislation. Indeed, this Bill, with some modifications, may have been acted upon favorably in both Houses by the time this report is published. If enacted, the measure will have far-reaching influence upon health services for children of school age, and therefore warrants close attention by pediatricians, general practitioners, health officers and others specially concerned in this area.

Section 2 of the Bill sets forth its general purpose as follows:

> In order that no American child shall come to adult life with physical or mental defects or conditions which can be prevented or corrected at an early age, it shall be the national policy to provide assistance to the several States to enable them to improve health services for school children for the prevention, diagnosis, and treatment of physical and mental defects and conditions of school children, with special reference to the correction of defects and conditions likely to interfere with the normal growth and development and educational progress of children. Such school health services shall utilize, insofar as feasible, the qualified health, medical, dental, and hospital facilities already established in each community.

An annual appropriation of $35,000,000 is proposed to carry out the purposes of the program. Federal funds would be allotted to the states according to a formula based on the child population and the relative per capita income. Under this formula, the lower

income states are allotted a higher amount per capita than the higher income states. Federal grants would be matched by state funds with a sliding scale, so that while the wealthiest would have to provide local funds equal to the Federal grant, the states with lowest per capita incomes would have to provide a sum equal to one third of the Federal sums, and other states varying amounts between these limits.

In order to obtain Federal funds for school health services, each state would be required to develop a comprehensive state plan, including certain services which are mandatory, and others which are optional.

Services which the state "shall provide"—those which are mandatory—are medical and dental examinations at periodic intervals for all school children in the state. This includes elementary and secondary schools, both private and public. It is stipulated that these examinations shall be conducted "insofar as practical at the schools which they attend." Also included as mandatory is the treatment of physical and mental defects for all children whose parents are unable to meet the necessary costs.

Worthy of particular note is an optional provision that the state "may provide for the prevention and treatment of such physical and mental defects and conditions for all school children." Thus, if the state so elects, it may set up service programs for the treatment of defects revealed by school health examinations irrespective of ability to pay. In part this provision is included in recognition of the fact that certain preventive and treatment services are now given in some states to all school children without regard to the financial status of their parents. In support of this provision, which obviously has enormous potential significance, the proponents of this Bill argue that it is not the place of the Federal Government to deny a state the right to provide such a program if it is deemed acceptable at the state level, particularly in the light of such programs already in existence.

The squabble between health and education agencies, which was largely responsible for defeating the School Health Services Bill a year ago, appears to have been resolved. On the Federal level, the Federal Security Administrator would administer this Act through the unit or units of the Federal Security Agency which he may designate. At the state level, the state is required to submit a plan "prepared by the State Educational Agency and the State Health Agency, jointly." Each state would then determine the division of responsibility between these agencies.

The Bill requires the state to utilize the qualified health, medical, dental, hospital and other related facilities already established in the state. Provision must also be made for cooperation with medical, dental, health and other organizations concerned and, where necessary, for working agreements with state and local public agencies having authority under state law for care of crippled children or physically handicapped children, or for other necessary health services. In submitting the report of the Senate Committee on Labor and Public Welfare, Senator Thomas stated:

> With regard to the actual treatment of defects and conditions shown by the health examinations, it is intended that appropriate referral procedures be developed, utilizing the existing qualified facilities and services, with due regard to the utilization of the services of family physicians and dentists, in a practicable manner designed to accomplish the purposes of this act.
>
> * * *

Under date of April 8, 1949, the bulletin published weekly from the Washington

office of the American Medical Association has this brief statement in reference to the School Health Services Bill: "The Bill was approved in principle. Several amendments were suggested, among them the function of the family physician."

It may also be noted that the Executive Board of the American Academy of Pediatrics meeting in Atlanta on April 16, 1949, approved S. 1411 in principle, with recommendation for certain amendments. Emphasis was directed to the need of including a statement requiring that school health programs should utilize the services of the family physician insofar as feasible. Secondly, it was recommended that the optional provision under which a state may be allowed to provide treatment for all children, irrespective of ability to pay, be deleted. For more detailed description of the official position of the Academy on S. 1411, reference may be made to the report of the Committee on Legislation approved by the Executive Board at the meeting referred to above.

JOSEPH S. WALL, M.D., *Chairman*
Committee on Legislation

INTERNATIONAL NEWS AND REPORTS

NEWS FROM ENGLAND

ALAN MONCRIEFF, M.D., *Corresponding Editor*

VITAL STATISTICS 1948

The provisional figures from the Registrar General for 1948 are remarkable for the lowest infant mortality rate for England and Wales ever recorded. This now stands at 34 per 1,000 related live births and is a big improvement on the previous lowest figure of 41 reached in 1947. The general death rate was also the lowest (10.8 per 1,000 total population) so that it is clear that the country has been experiencing a healthy year. It has been suggested that the academic developments of child health departments in nearly all the universities in the past few years may be allotted some share in the credit for the record infant mortality rate.

BCG

Distinguished up until the present for being one of the few major countries with no first hand experience of BCG vaccination against tuberculosis, Great Britain is about to embark upon national trials. Exact details are not yet available but it is understood that it is to be on a voluntary basis for medical students and nurses as one group and for young children in contact with open tuberculosis in their homes. Pediatricians are naturally greatly concerned with these last and will want to see a carefully controlled scheme worked out. There is so much presumptive evidence and relatively little that is scientifically completely acceptable.

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

LEONA BAUMGARTNER, M.D., *Contributing Editor*

A "MEASLES YEAR"

ACCORDING to the reports of the U.S. Public Health Service, this is a measles year. For example, a total of 15,266 cases were reported for the week of January 29, 1949, compared to a five year median of 6,712. Increases were reported in all geographic divisions except New England and the West North Central area. The largest increases were in the East South Central and South Atlantic areas. Of the total that week, an aggregate of 10,522 cases occurred in the following 12 states: Massachusetts, New York, Pennsylvania, Michigan, Wisconsin, Maryland, Virginia, Kentucky, Alabama, Texas, Oregon, and California.

In contrast to measles, the influenza incidence picture shows an unusually low number of cases. For example, in the week of January 29, 1949, a total of 4,534 cases was reported, compared to a five year median of 14,253.

LIST OF PUBLICATIONS

Under date of March 1948 the Children's Bureau has published a list of its publications. The list includes all publications of the Children's Bureau issued since 1945 that are available for general distribution; earlier publications of the Bureau that are still available and of current value; some reprints of material published elsewhere but reproduced by or for the Bureau. Pediatricians will find some of these reprints of particular interest. Single copies of the list and of most of the publications can be obtained free from the Children's Bureau, Washington 25, D.C.

NEWS AND ANNOUNCEMENTS

Dr. Martha Eliot in U. N. Health Job

The appointment of Dr. Martha Eliot, Associate Chief of the Children's Bureau, as Assistant Director General of the United Nations World Health Organization has been announced both in Washington and Geneva.

It was also announced that Dr. Eliot had resigned from the Children's Bureau, which she had served for 25 years, and that Dr. Leona Baumgartner, on 6 months' leave as Assistant Commissioner of Health, New York City, has been appointed as Associate Chief of the Children's Bureau to fill Dr. Eliot's place.

Dr. Eliot will go to Geneva, headquarters of the world organization and Dr. Baumgartner will come to Washington June 1.

Dr. Eliot's appointment was made by Dr. Brock Chisholm of Canada, Director General of the World Health Organization. Dr. Eliot had been one of the leaders in the health group from its earliest planning stages, and as a United States delegate was the only woman to sign its constitution. At the permanent organization meeting in Geneva in 1948, Dr. Eliot won the inclusion of a maternal and child health program in the operations of the health organization.

* * *

Appointment of Dr. Glidden L. Brooks as associate director of the American Academy of Pediatrics' Committee for the Improvement of Child Health, whose offices are in Philadelphia, was announced today by Dr. Warren R. Sisson, president of the Academy. Dr. Brooks has been executive director and chief of pediatrics of the Central Maine General Hospital, Lewiston, Maine; during the period 1944 to 1945, he was assigned to active duty with the U. S. Public Health Service.

In his post, Dr. Brooks will aid in developing an action program for the nationwide improvement of child health based on a 3 year study of child health services just completed by the Academy with the cooperation of the U. S. Public Health Service and the Children's Bureau.

* * *

Second Pan-American Congress of Pediatrics

Announcement has been made of the Second Pan-American Congress of Pediatrics to be held in Mexico City, Nov. 2-5, 1949. This Congress will follow the Third National Congress of Pediatrics which will be held Oct. 30-Nov. 1, 1949 in Mexico City.

Honorary President: Miguel Aleman, President of Mexico.

Dr. Federico Gómez, Director of the Hospital Infantil of Mexico City, appointed by the First Pan-American Congress as President of the Organizing Committee of the Second Pan-American Congress, and appointed by the Mexican Society of Pediatrics in the same capacity for the Third National Congress, together with Drs. Rafael Soto, Secretary, and Luis Berlanga Berumen, Treasurer, has appointed one Committee for both Congresses, as follows: President: Dr. Federico Gómez; Vice-President: Dr. Jesús Lozoya; Secretaries: Drs. Rafael Soto, Alejandro Aguirre, Antonio Prado Vértiz and Julia Baker; Secretary of Activities: Dr. Ismael Martínez Sotomayor; Pro-Secretaries: Drs. Lazaro Benavides and Manuel Mendez; Treasurers: Drs. Hermilo Castañeda and Luis Berlanga Berumen; Reporter: Dr. Pedro Daniel Martínez. The program includes plenary and sectional sessions. Requests for places on the sectional sessions must be addressed to:

Dr. Alejandro Aguirre, Secretary
Second Pan-American Congress of Pediatrics
Hospital Infantil
Mexico City, Mexico

* * *

Medical Continuation Courses—University of Minnesota

The University of Minnesota Medical School offers for physicians a course in the Basic Medical Sciences and Their Clinical Correlation. This course is particularly suggested for those physicans

who have had clinical or hospital training to fulfill the requirements of specialty boards and who wish approved training in the basic medical sciences.

PROGRAM

Fall Quarter, Sept. 26 to Dec. 17, 1949.

Subjects: Blood and Blood-forming Organs, Digestive System, Metabolism and Nutrition, Endocrinology and Cardiovascular System.

Winter Quarter, Jan. 4 to March 18, 1950.

Subjects: Respiratory System, Urinary Tract, Nervous System, Locomotor System and Infectious Diseases.

The Center for Continuation Study of the University of Minnesota also announces a series of shorter, more intensive courses for graduate physicians. The following courses will be presented during the year 1949-50:

Anesthesiology
Cancer Control
Cardiovascular Diseases
Child Psychiatry
Dermatology
Internal Medicine
Neurology
Obstetrics
Otorhinolaryngology
Pediatrics
Pediatric Radiology
Proctology
Psychiatry
Surgery

For further information regarding any of these courses, write to:

Director, Postgraduate Medical Education
Center for Continuation Study
University of Minnesota
Minneapolis 14, Minn.

* * *

The American Board of Pediatrics announces the following dates for the coming Examinations by the Board during 1949. Written Examinations under local Monitors will be held on Friday, June 24, 1949, from 2:00 to 4:00 p.m.

Oral Examinations will be held as follows:

Cleveland, Ohio—Sept. 16, 17 and 18, 1949
New York, N.Y.—Oct. 21, 22 and 23, 1949
Chicago, Ill.—Dec. 9, 10 and 11, 1949

* * *

Dr. Harold K. Faber, Professor of Pediatrics at Stanford University, San Francisco, Calif., will resign his position on July 1, 1949 and become Professor Emeritus.

Dr. John A. Anderson, Professor and Head of Department of Pediatrics, University of Utah, College of Medicine, will succeed Dr. Faber.

* * *

Dr. Lillian R. Smith died at her home, Harwich, Mass., on April 13. She was formerly director of the State of Michigan's Bureau of Maternal Health and Child Hygiene, and also director of the EMIC program in Michigan. She was a fellow of the Academy.

BOOK REVIEWS

VIRAL AND RICKETTSIAL INFECTIONS OF MAN, Edited by Thomas M. Rivers, Philadelphia, J. B. Lippincott Company, 1948.

It has been the practice in the past that viral and rickettsial agents and the diseases caused by them were included in textbooks of bacteriology. Thus these chapters were written by authors who frequently were not experts in this field. Furthermore, the various aspects of these diseases often are sufficiently different from those caused by bacterial organisms to warrant separate treatment. This separation has been accomplished in "Viral and Rickettsial Infections of Man," edited by Thomas M. Rivers, and its companion "Bacterial and Mycotic Infections of Man," edited by René J. Dubos.

This volume is clearly intended as a textbook for medical students and practicing physicians, and consequently deals only with the well established facts of virology, whereas material of a more problematic nature has been largely avoided. To accomplish this with the greatest efficiency, 27 experts in the various fields of virology have participated in a cooperative effort. Although much may be gained by such a distribution of talent, it will be difficult on the other hand for the individual author to be completely unbiased in the evaluation of his own special field. It is to the credit of this enterprise that few objections of this nature can be raised.

The first chapters deal with the general principles of viral and rickettsial infections, concerning pathology, immunity transmission, prevention and epidemiology, the nature, the physical and chemical properties of these agents, the serologic reactions employed in their identification and in the diagnosis of the diseases and, finally, the technics used for propagation of the agents in the chick embryo and in tissue culture. Since "isolation" of virus in experimental animals, likewise, constitutes a technic of major importance, a chapter of this subject would not have been amiss.

The subsequent chapters deal with individual groups of agents or diseases. As one might expect from the impressive list of contributors they are all authoritatively treated and sum up the present knowledge based upon well established facts. It is obvious that it cannot be the purpose of a volume like this to support every statement with references and only major contributions are thus ascribed to their authors. However, it is difficult to see, as an example, how a chapter on influenza can be complete without mention of the name of Richard E. Shope.

As the title implies, emphasis has been placed on diseases of man. Nevertheless, a chapter is included on bacterial viruses obviously on account of the many valuable contributions derived from this field toward our understanding of viruses in general. Since this one exception has been made one might wonder whether another concerning tumor viruses would not have been equally valuable. An authoritative discussion of this field would certainly be of benefit to the medical student who now may seek that information from other, possibly less enlightened, sources.

These few suggestions offered by the reviewer do not and should not deter from the excellence of this volume. There is no doubt that it is a valuable and much needed addition to the medical library.

WERNER HENLE

CHILD HEALTH SERVICES AND PEDIATRIC EDUCATION; Report of the American Academy of Pediatrics, Commonwealth Fund, New York, 1949, $3.50, 270 pp.

The American Academy of Pediatrics has made a nation-wide survey, the first ever undertaken, of all the services and facilities currently available for the medical care and health supervision of infants and children throughout the country. And, because the quality of the health services is largely dependent on the pediatric orientation of the physician, the second half of this study is devoted to an analysis of present-day pediatric education.

In the conduct of the study and the analysis of the data, the Academy has had the cooperation of the U.S. Public Health Service and the U.S. Children's Bureau. The study has been carried out state-by-state and county-by-county under supervision of state chairmen of the Academy with the cooperation of state and county medical societies and local health departments.

The findings of this statistical survey are presented here in 106 charts and diagrams which cover

the services of physicians and dentists in private practice, of hospitals and community health agencies, both official and voluntary as well as of pediatric education. A supplementary volume, now in press, will present in tabular form more of the data on which this book is based.

OBSTETRIC ANALGESIA AND ANESTHESIA, Franklin F. Snyder, M.D., Philadelphia, W. B. Saunders Company, 1949.

This book is an excellently developed presentation of the present status of pain-relieving drugs in obstetrics. It is divided into two sections: The first is devoted to (1) detailed analysis of clinical and experimental data referrable to fetal respiration, and (2) pathologic pulmonary conditions in the fetus and newborn that might be causally related to the labor inhibiting and respiratory depressive effects of many, if not all, the pain-relieving drugs used during delivery. The scope of the section is indicated by some of the chapter headings, i.e., incidence of respiratory injury before birth; respirations before birth; intrauterine pneumonia; atelectasis; asphyxia.

The second section includes a detailed discussion of each of the commonly used pain-relieving drugs and procedures in obstetrics. Each drug is described as to historical aspects, pharmacology (effect on progress of labor and on the fetus), toxicology, dosage as well as clinical applications.

Each chapter in both sections has its own complete summary and bibliography, much of which is of recent origin. An interesting addition is a chapter on experimental methods for evaluating the effects of various anesthetic agents upon the mother and child, thus supplementing much of the clinical experience with the results of animal experimentation.

A noteworthy omission for a book of this kind, in the reviewer's opinion, is the lack of any mention of the recent interest in the psychogenic approach to the problem of pain control during delivery.

HERMAN YANNET

PARENT AND CHILD, Catherine Mackenzie, New York, William Sloane Associates, Inc., 1949, $2.95, 333 pp.

This somewhat unusual book on parent education concerning children is a compendium of advice assembled from the author's experience as a reporter in this field. It is made up of analysis and reviews of published interviews with many people specializing in child health and care. The text is well written, well above the intelligence and understanding of many parents, at about the same level as the newspaper the author represents. It is a good book for pediatricians and doctors, who will find a great deal of useful information in it.

GIVE THEM A CHANCE TO TALK, Berneice R. Rutherford, M.S., Minneapolis 15, Minn., Burgess Publishing Company, 1948, $2.75, 116 pps., 9 illustrations.

This is a small cardboard covered handbook in photo-offset print, designed mainly for the speech therapist working with children handicapped by cerebral palsy. It contains a brief description of cerebral palsy (athetoid, spastic and ataxic), classification and description of the common speech disorders, an outline of the sequences of speech development together with a guide to the assessment of speech (articulatory) maturity, and a description of speech and sound discrimination tests.

A detailed outline of the methods of speech therapy used in the athetoid, the spastic, and the ataxic child follows. Mrs. Rutherford's principle of therapy is to begin with the stage of articulatory development which the child has attained, and continue through the normal developmental sequences toward normal speech. Her methods include exercises to strengthen the muscles used in speech and to develop the child's awareness of these muscles, elimination of undesirable postures and accessory movements, practice in word formation and language building with emphasis upon meaning, and utilization of special training devices for the improvement of quality of speech, such as rate, rhythm, pitch and intensity. The simplicity and detail of the specific instructions for therapeutic training are excellent. Admittedly and advisedly the program is adapted to suit the needs of the individual child. The important question of the motivation of the child is only briefly mentioned and could well have received more attention. There is no statement of the results achieved by treatment.

A final chapter gives some consideration to the development of a satisfactory emotional and social adjustment in the child with cerebral palsy, but the problems involved are barely suggested; those of the parents are not even mentioned.

For the speech therapist this should be a very useful book, and it is the only one, to our knowledge, devoted almost exclusively to speech training in cerebral palsy. For the pediatrician unfamiliar with the methods of speech help for the child with cerebral palsy, it is an excellent guide and reference, either for observation or supervision of therapy. It could not be used by the average parent without the close supervision of a speech therapist.

RUTH W. METRAUX and
CATHERINE S. AMATRUDA

PEDIATRICS AND THE EMOTIONAL NEEDS OF THE CHILD, edited by Helen L. Witmer, New York, Commonwealth Fund, 1948, $1.50, 180 pp.

This short selective account of the Conference at Hershey, Pennsylvania in March 1947 of 44 pediatricians, psychiatrists, and psychiatric social workers, gathered at the invitation of the Commonwealth Fund, asks many questions and offers many suggestions regarding the teaching of and the experimental approach to comprehensive pediatrics. In a number of papers and considerable discussion the definition of the work and training of the pediatrician with psychologic insight was suggested. In considering what is known of emotional and physical growth and development, and the pediatrician's place in mental health, the participants offered new ways of training medical students, doctors, nurses and social workers so as to secure greater insight and integration among these allied disciplines. Great as are the advantages of special projects for longitudinal study of the child, a belief prevailed that existing pediatric, psychiatric, and social service agencies, through closer collaboration and heightened awareness of a common purpose can make meaningful contributions to research in the field of total development, at the same time increasing the psychologic astuteness of practitioners. In demonstration of such collaboration the members of this conference set a productive precedent.

SIDNEY J. LASELL

HOW TO HELP YOUR CHILD GROW UP, Angelo Patri, Chicago, Rand McNally & Company, $4.00, 340 pp.

It is a pleasure to receive and recommend this book and to know that the short chapters published as syndicated articles in the daily press have been made available in permanent form. The use of these short chapters, repeated frequently in small doses, is one of the effective methods of bringing home to parents good advice on child behavior and the approach to the problems and questions related thereto. There are many who would like to have a permanent record of the press articles.

The book is a continuation of several books under varied titles, made up of the same subject matter. The text is made up of seven parts—The Child Himself—The Baby—The Child at Home—The Child at School—Growing into Youth—and Suggestions for Special Problems. Each part is subdivided into chapters, made up of an introductory statement, then an arrangement of short topics, each with a special note. There are no illustrations and none are needed for this book. There is a good index.

The best topic, Number 48, "The Record" is worth the effort of every parent, teacher, physician, nurse and anyone concerned with studying and solving problems of child behavior. "The Record" is just as important as any scientific study in a laboratory.

HUGH MCCULLOCH

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